UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2012

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

2855 Gazelle Court, Carlsbad, CA 92010
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act: **Common Stock, $.001 Par Value**

Indicate by check mark whether the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes x No o

Indicate by check mark whether the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No x

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer x	Accelerated filer o
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes o No x

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Select Market was $1,011,059,448 as of June 30, 2012.*

The number of shares of voting common stock outstanding as of February 21, 2013 was 101,826,748.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 26, 2013 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 25, 2013 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 75 to 79 incorporates several documents by reference as indicated therein.

* Excludes 16,065,491 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 2012. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis

Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

In this report, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO™ is a trademark of Genzyme Corporation

KYNAMRO Cornerstone℠ is a service mark of Genzyme Corporation

Macugen® is a registered trademark of Eyetech

Juxtapid™ is a trademark of Aegerion Pharmaceuticals, Inc.

CORPORATE INFORMATION

We incorporated in California in 1989, and in January 1991 we changed our state of incorporation to Delaware. Our principal offices are in Carlsbad, California. We make available, free of charge, on our website, *www.isispharm.com*, our reports on Forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference. You may also read and copy our filings at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

PART I

Item 1. Business

Overview

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. Our strategy is to do what we do best—to discover unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer. Our partnering strategy provides us the flexibility to license each of our drugs at the optimal time to maximize the near- and long-term value of each drug. In this way, we can expand our pipeline and our partners' pipelines with antisense drugs that address significant medical needs while remaining small and focused. Our strong financial position is a result of the successful execution of our business strategy as well as our focused research and development capabilities.

Our flagship product, KYNAMRO™ (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the U.S. Food and Drug Administration, or FDA, approved the marketing application for KYNAMRO for patients with HoFH. Marketing applications for KYNAMRO are under review by the European Medicines Agency, or EMA, and other regulatory authorities. Genzyme is executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally

for severe and rare diseases and plans to leverage its infrastructure in these markets. By concentrating marketing and sales efforts on lipid specialists and physicians who refer patients to these specialists, Genzyme plans to quickly reach patients with HoFH in the United States.

Our pipeline goes well beyond KYNAMRO. We have a pipeline of 28 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We believe that several of the drugs in our pipeline could reach the market in the next five years. For instance, we designed our TTR amyloidosis and spinal muscular atrophy, or SMA, drugs to treat patients with severe and rare diseases who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. In addition, several of the drugs in our pipeline are advancing through Phase 2 clinical programs and could represent significant near-term licensing opportunities. These drugs, including ISIS-APOCIII$_{Rx}$, ISIS-CRP$_{Rx}$ and ISIS-FXI$_{Rx}$, represent substantial commercial opportunities with the potential for robust Phase 2 data within the next 12 to 18 months.

To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec and GlaxoSmithKline, or GSK, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk,

like rare diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. This strategy allows us to develop drugs that could have significant commercial potential with a knowledgeable and committed partner while avoiding the cost of later-stage clinical studies. As in all of our partnerships, we benefit financially from upfront payments, development, regulatory and commercial milestones, licensing fees and royalties from these partnerships. This allows us to expand and broaden our drug discovery efforts to new disease targets in therapeutic areas that are outside of our expertise or in areas where our partners will provide tools and resources that will complement our drug discovery efforts. For example, through our oncology partnership with AstraZeneca, we are capitalizing on AstraZeneca's development experience and research in oncology.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. For example, in 2012, we formed three strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, and a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer. In total during 2012, we received $96 million from Biogen Idec and AstraZeneca in upfront payments and have the potential to earn more than $2 billion in future milestone payments and licensing fees. Since 2007, our partnerships have generated an aggregate of more than $975 million in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our current partnered programs we have the potential to earn $5.1 billion in future milestone payments. We also have the potential to share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, or royalty arrangements.

We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we co-founded with Alnylam focused on microRNA therapeutics. In October 2012 Regulus completed an initial public offering, in which we participated, bringing our ownership in Regulus to approximately seven million shares of Regulus' common stock, which was valued at approximately $36 million on February 26, 2013. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

We protect our proprietary technologies and products through our substantial patent estate. As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated over $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Below is a list of some of our key accomplishments for 2012 and early 2013.

Drug Development Highlights

- We and Genzyme were successful in bringing KYNAMRO to the market for patients with HoFH. These patients are at high cardiovascular risk and may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
  - KYNAMRO was approved for marketing in the United States by the FDA for the treatment of patients with HoFH.
    - We received a total of $50 million in milestone payments from Genzyme related to the new drug application, or NDA, acceptance in 2012 and marketing approval of KYNAMRO by the FDA in 2013.
  - Genzyme continues to enroll the FOCUS FH study, which is designed to provide 60-week safety and efficacy data in familial hypercholesterolemia, or FH, patients to support an additional regulatory filing. Genzyme reached an agreement with the FDA on the design of the FOCUS FH study via a Special Protocol Assessment, or SPA.
  - Genzyme submitted a request for re-examination of the EMA's negative opinion on the marketing authorization application for KYNAMRO and expects to report the outcome of the re-examination in the first half of 2013.
  - We received European Good Manufacturing Practices, or GMP, certification of our manufacturing facility for production of drug substance to support KYNAMRO commercial launch.
  - Clinical investigators presented KYNAMRO data at important cardiovascular medical meetings throughout the year.
    - Dr. Raul Santos presented data from the long-term extension study of KYNAMRO at the International Symposium on Atherosclerosis. These data highlighted the long-term safety and efficacy of KYNAMRO in patients who have been treated with KYNAMRO.
    - Dr. Klaus Parhofer presented an analysis of data from the KYNAMRO Phase 3 study in patients with severe heterozygous FH at the European Society of Cardiology. These data highlighted the potential of KYNAMRO to reduce the need for apheresis by lowering LDL-C values below the thresholds for apheresis eligibility in patients with severe heterozygous FH.
    - Dr. Sotirios Tsimikas presented an analysis of lipoprotein a, or Lp(a), data from the KYNAMRO Phase 3 program at the European Atherosclerosis Society. These data demonstrated sustained reductions of Lp(a), an independent risk factor for cardiovascular disease.
- We and our partners reported positive clinical data on seven drugs and we added four drugs to our pipeline.
- We and our partners initiated Phase 2 or Phase 3 clinical studies on eight drugs.
- We received Orphan Drug Designation and Fast Track Status in the United States for ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. We received Orphan Drug Designation in the EU for ISIS-SMN$_{Rx}$.

Corporate Highlights

- We formed three new strategic alliances with Biogen Idec to develop and commercialize antisense drugs for severe and rare and neurologic diseases. In total all three alliances are valued at up to $1.2 billion.
  - We entered into an alliance with Biogen Idec to develop and commercialize our drug, ISIS-SMN$_{Rx}$, to treat SMA. We received a $29 million upfront payment and are eligible to receive up to an additional $270 million in a license fee and milestone payments, and double-digit royalties on sales of ISIS-SMN$_{Rx}$.
  - We entered into an alliance with Biogen Idec to develop and commercialize a drug to treat myotonic dystrophy type 1, or DM1. We received a $12 million upfront payment and are eligible to receive up to an additional $259 million in a licensing fee and milestone payments. We are also eligible to receive double-digit royalties on product sales.
  - We entered into an alliance with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. We received a $30 million upfront payment and are eligible to receive up to another $200 million in a license fee and regulatory milestone payments per program. We are also eligible to receive double-digit royalties on product sales for each drug.

- We formed a new strategic alliance with AstraZeneca to discover and develop antisense drugs against five cancer targets, which included a license to develop and commercialize ISIS-STAT3$_{Rx}$.
  - The agreement comprises $31 million in upfront and near-term payments, including a $25 million payment we have received followed by a $6 million payment we are eligible to receive in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees and royalties.
  - We added the first drug from the research collaboration, ISIS-AZ1$_{Rx}$, to the pipeline.
- We and GlaxoSmithKline amended the clinical development plan and financial terms relating to ISIS-TTR$_{Rx}$ to support an accelerated development plan for the drug. As a result of the revised agreement, we received a $2.5 million upfront payment.
  - We received a $7.5 million milestone payment upon initiation of the Phase 2/3 study for ISIS-TTR$_{Rx}$.
  - We are also eligible to earn an additional $50 million in pre-licensing milestone payments to support the ISIS-TTR$_{Rx}$ Phase 2/3 study.
- We benefited as our partners advanced RNA-based technologies and products incorporating our technology.
  - We received $2.7 million from Alnylam as a result of Alnylam's licenses that included our patents.
  - We received $1.3 million from Pfizer triggered by Pfizer's decision to advance EXC 001 into a Phase 2 study.

- Regulus Therapeutics completed an initial public offering and is now traded on The NASDAQ Global Market under the ticker RGLS. We purchased $3 million of Regulus' common stock at the offering price and remain a significant shareholder with approximately 17 percent ownership on a fully diluted basis, which was valued at approximately $36 million on February 26, 2013.
- We completed a successful $201.3 million convertible debt financing. We used the majority of the proceeds of this financing to redeem our outstanding $162.5 million 2 $^{5}/_{8}$ percent subordinated convertible debt.
- The securities class action lawsuit was voluntarily withdrawn and there are no pending lawsuits related to any violation of securities laws.
- We and our collaborators published papers in leading scientific journals demonstrating the broad applicability of our technologies.
  - A paper in Nature demonstrating that an antisense compound selectively and rapidly reduced target RNA in skeletal muscle and alleviated disease in animal models of myotonic dystrophy.
  - A paper in Neuron demonstrating that an antisense compound reversed disease in animal models of Huntington's disease.
  - Two papers in the journal Cell demonstrating that single-stranded RNA-like antisense technology can activate the RNAi pathway and inhibit the expression of targeted genes.

Drug Discovery and Development

Introduction to Drug Discovery

Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production or improper protein activity. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense drugs are different from traditional small molecule drugs because they interrupt the production of disease-causing proteins by targeting ribonucleic acids, or RNAs. RNAs are naturally occurring molecules in the body that provide the information the cell needs to produce proteins. When our antisense drugs bind to the specific RNAs of a particular gene, they will ultimately inhibit or alter the expression of the protein encoded in the target gene.

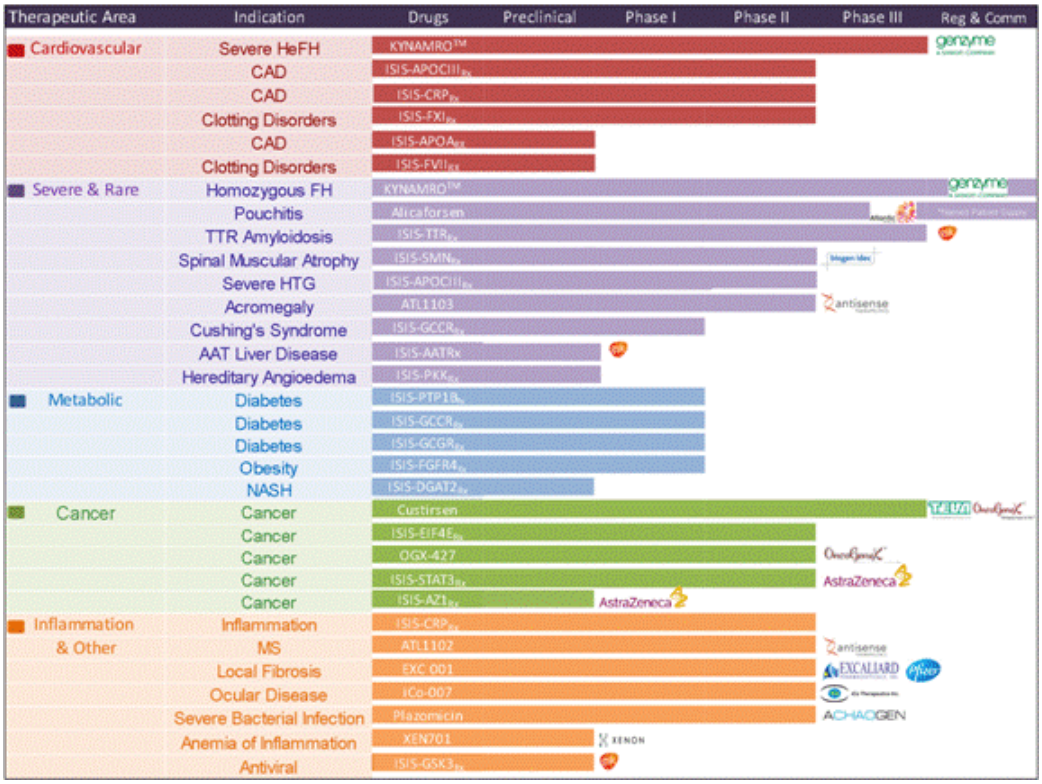
Our Development Projects

We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets, we can build a large and diverse portfolio of drugs designed to treat a variety of health conditions, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer. We and our partners are developing antisense drugs for systemic, intrathecal and local delivery. We expect to continue to add new drugs to our pipeline, creating opportunities for future licensing transactions and building a broad proprietary portfolio of drugs applicable to many disease targets. We also continue to improve our scientific understanding of our drugs, including how our drugs impact the biological processes of the diseases we target.

With our expertise in discovering and characterizing novel antisense inhibitors, our scientists can optimize the properties of our antisense drugs for use with particular targets. Our scientists have made significant advances in chemistries, which we call our second-generation antisense drugs. Second-generation antisense drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. Our scientists have further improved upon our second-generation chemistry with our generation 2.5 chemistry, an advancement that we believe will further increase the potency of our drugs and make oral administration commercially feasible. We currently have two generation 2.5 drugs in development, ISIS-STAT3$_{Rx}$ and ISIS-FVII$_{Rx}$, and we expect that some of our future drugs will also incorporate our generation 2.5 chemistry.

Our scientists have utilized our chemistry advancements to expand the therapeutic and commercial opportunities of our pipeline. These advancements, along with the manufacturing and analytical processes that are the same for all of our drugs, shorten our timeline from initial concept to the first human dose when compared to small molecule drugs.

The following table lists our approved products and each of our and our partners' drug development projects, their targets, disease indications and the development status of each. Prior to Phase 3 studies, we identify our drugs by the target, such as ISIS-GCGR$_{Rx}$ or ISIS-APOCIII$_{Rx}$. For the majority of our partnered drugs, we refer to a drug by the partner's own compound number, such as ATL1103 or iCo-007. As the drugs in our pipeline advance in clinical development, we will adopt nonproprietary names given to each drug from the United States Adopted Names Council. For example, mipomersen is a nonproprietary name that we obtained for ISIS 301012 in 2007. Once we or our partners establish a brand name, like KYNAMRO for mipomersen, we will adopt the brand name even before regulatory agencies grant marketing approval.



KYNAMRO (mipomersen sodium) injection

Our flagship product, KYNAMRO, is on the market in the United States for patients with HoFH. These are patients who are at high cardiovascular risk and who may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies. KYNAMRO was approved by the FDA as an adjunct to lipid-lowering therapy and diet to reduce LDL-C, apolipoprotein-B, or apo-B, total cholesterol and non-HDL-C in patients with HoFH. KYNAMRO is available in the United States under a Risk Evaluation and Mitigation Strategy, or REMS, with a Boxed Warning citing the risk of hepatic toxicity.

Genzyme is also pursuing marketing approval for KYNAMRO in other major markets. Genzyme is executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and plans to leverage its infrastructure in these markets. Beyond the United States, KYNAMRO is under review by the EMA and other regulatory authorities.

We believe that Genzyme has the commercial infrastructure and ability to successfully commercialize KYNAMRO worldwide making the drug available for patients in need in approved markets. By concentrating marketing and sales efforts on lipid specialists and physicians who refer patients to these specialists, Genzyme plans to reach patients with HoFH in the United States. Genzyme has also established KYNAMRO Cornerstone[SM], a support program for health care providers, patients, families and caregivers that offers services related to HoFH and KYNAMRO in the United States. Along with preparing for an efficient marketing and sales effort for KYNAMRO, Genzyme has made significant progress raising awareness of HoFH, and the importance of family screening to identify patients earlier. These activities include conducting continued medical educational programs to inform physicians about FH and partnering with key advocacy groups, such as the National Lipid Association, American College of Cardiology, European Atherosclerosis Society Congress, International Symposium on Atherosclerosis and the American Heart Association. In 2011, Sanofi acquired Genzyme, and we believe that Sanofi and its global presence will aid in the rapid market expansion of KYNAMRO throughout the world.

KYNAMRO is a novel, first-in-class, apo-B synthesis inhibitor for the reduction of LDL-C. It is a second-generation antisense drug we discovered and licensed to Genzyme in 2008. KYNAMRO acts by decreasing the production of apo-B. Apo-B provides the structural core for atherogenic lipids, including LDL-C, which carry cholesterol through the bloodstream. KYNAMRO reduces LDL-C and other key atherogenic lipids linked to cardiovascular disease by preventing their formation. Together with Genzyme, we completed the largest clinical study conducted to date in HoFH patients. In the randomized, double-blind, placebo controlled, multi-center trial, KYNAMRO significantly further reduced LDL-C and all other measured endpoints when added to a treated baseline. Three patients (12 percent) treated with KYNAMRO withdrew due to adverse events. Consistent with other studies evaluating KYNAMRO, commonly observed adverse events included mild to moderate injection site reactions and flu-like symptoms, as well as elevations in liver transaminases.

Familial Hypercholesterolemia

Physicians diagnose patients as having FH if they have very high cholesterol, are at high cardiovascular risk and cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. FH is a genetic disease that causes elevated LDL-C levels and family patterns of premature heart disease and heart disease-related death. FH patients have inherited abnormalities in liver cells that are responsible for clearing LDL particles from the blood. FH is autosomal dominant, which means that all first-degree relatives of FH patients have a 50 percent chance of having the disease as well, making early detection through early screening critically important. Patients with untreated FH have a 50 percent mortality rate by age 60.

HoFH is a severe form of FH. People with HoFH have inherited mutations that limit the body's ability to clear cholesterol. HoFH is extremely rare: it is believed to occur in only one out of every one million persons. As with other rare diseases, the true prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis. Today, it is estimated that HoFH affects about 6,000 people globally. Medical literature includes different criteria for making an HoFH diagnosis. HoFH may be diagnosed by clinical or genetic parameters, and may be considered in cases of unusually high LDL-C, such as

greater than 500 mg/dL without treatment, or 300 mg/dL after taking cholesterol-lowering medication. Because HoFH is genetic, it is important that all family members of people with HoFH know their cholesterol levels, regardless of their age. In addition to lipid-lowering medications, current standard-of-care for HoFH patients can include apheresis, a two to four hour process administered two to four times a month. Apheresis mechanically separates LDL-C from the blood and it has been the only therapy available on top of maximally tolerated lipid-lowering therapy.

Clinical Development

Together with Genzyme, we evaluated KYNAMRO in a Phase 3 study in patients with HoFH. The randomized, double-blind, placebo-controlled, multi-center study enrolled 51 HoFH patients age 12 to 53 years, including seven patients age 12 to 16 years, who were maintaining a regimen of maximally tolerated lipid-lowering medications. Treatment with KYNAMRO further reduced LDL-C levels by an average of 113 mg/dL, or 25 percent, from a treated baseline of 439 mg/dL, and further reduced all measured endpoints for atherogenic particles. In March 2010, these data were published in The Lancet by Professor Raul of the University of the Witwatersrand in South Africa.

Together with Genzyme we also conducted three additional Phase 3 studies in patients with severe hypercholesterolemia, in patients with heterozygous familial hypercholesterolemia, or HeFH, and in patients with high cholesterol at high risk for cardiovascular disease. In all three Phase 3 studies, treatment with KYNAMRO lowered LDL-C and reduced other atherogenic lipids, including apo-B, total cholesterol, non-HDL-C, and Lp(a). These key lipids are generally accepted risk factors for cardiovascular disease. Data from these studies were published in Circulation and PLoS One.

Safety data for KYNAMRO are based on pooled results from the four Phase 3 studies noted above with a total of 390 patients. In these four Phase 3 studies, 261 patients received weekly subcutaneous injections of 200 mg of KYNAMRO and 129 patients received placebo for a median treatment duration of 25 weeks. Eighteen percent of patients on KYNAMRO and 2 percent of patients on placebo discontinued treatment due to adverse reactions. The most common adverse reactions in patients treated with KYNAMRO that led to treatment discontinuation and occurred at a rate greater than placebo were: injection site reactions of five percent, alanine aminotransferase increase of 3.4 percent, flu-like symptoms of 2.7 percent, aspartate aminotransferase increase of 2.3 percent and abnormal liver function test of 1.5 percent.

Based on these positive data, Genzyme submitted an NDA to the FDA in March 2012 for marketing approval of KYNAMRO in patients with HoFH. In January 2013, the FDA approved the NDA for KYNAMRO. In 2011, Genzyme submitted a marketing authorization application, or MAA, for KYNAMRO to the EMA. In December 2012, the Committee for Medicinal Products for Human Use, or CHMP, of the EMA adopted a negative opinion for the MAA for KYNAMRO. Genzyme requested a reexamination of the CHMP opinion and expects to report the outcome of the re-examination in the first half of 2013. Genzyme has also submitted marketing applications for KYNAMRO in other countries.

In March 2012, Genzyme and we reported data from a Phase 3 long-term extension study of KYNAMRO. Data from this study included 141 patients who enrolled in the study after having completed one of the three Phase 3 studies: HoFH, severe hypercholesterolemia, or the HeFH study. In this study, patients treated with KYNAMRO for two years maintained robust reductions in LDL-C and all other apoB-containing atherogenic lipoproteins measured with a safety profile consistent with the completed Phase 3 studies of KYNAMRO.

In 2012, Genzyme initiated a Phase 3 study titled ‘evaluating the saFety and atherOgeniC lipoprotein redUction of mipomerSen in FH, or FOCUS FH, which Genzyme is conducting under an SPA with the FDA. An SPA is an agreement between the FDA and the drug developer that the design and planned analysis of a study is sufficient to address objectives in support of a regulatory submission. In FOCUS FH, Genzyme is evaluating KYNAMRO in patients with severe heterozygous FH. Severe HeFH patients are defined as FH patients who have LDL-C levels greater than 200 mg/dL with coronary artery disease or more than 300 mg/dL without coronary artery disease despite maintaining a regimen of maximally tolerated lipid-lowering therapy. In this 60-week, placebo-controlled, randomized, double-blind study, KYNAMRO is being administered either weekly as a 200 mg injection or three times a week as a 70 mg injection.

Cardiovascular Franchise

Cardiovascular disease is the leading cause of death in the United States. A common cause of cardiovascular disease is atherosclerosis, or premature plaque buildup, which occurs when cholesterol and inflammatory cells accumulate in blood vessels. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. As such, lowering cholesterol is a key component in preventing and managing cardiovascular disease.

Cardiovascular disease is an area of focus for us. We have created a cardiovascular disease franchise comprised of drugs that target all the key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis, an aberrant blood clot formation responsible for most heart attacks and strokes. For example, we are developing a drug that lowers apoC-III and triglycerides, which are both independent risk factors for cardiovascular disease. Our most recent addition to our cardiovascular franchise is our drug that lowers Lp(a), another independent risk factor for cardiovascular disease. Currently available lipid-lowering therapies do not significantly lower apoC-III, triglycerides, or Lp(a). We believe that targeting apoC-III and Lp(a) could provide a complementary approach to lipid-lowering therapies, including KYNAMRO. We are also developing a drug that lowers C-reactive protein, or CRP, a protein that scientists associate with cardiovascular disease. And finally, our cardiovascular franchise includes two anti-thrombotic agents, which could offer safer, more effective alternatives to anti-clotting agents currently on the market.

We believe antisense drugs could have a significant positive effect in patients with high cardiovascular risk. Because there are many liver-produced targets that affect the production of cholesterol particles, clotting factors and other factors that contribute to the inflammatory components of cardiovascular disease, the liver is an ideal target organ for cardiovascular disease therapies, and antisense drugs in particular. Our antisense drugs distribute to the liver and inhibit the production of many targets associated with cardiovascular risk, creating an opportunity for us to develop many complementary and effective antisense drugs for cardiovascular disease.

ISIS-APOCIII$_{Rx}$ — ISIS-APOCIII$_{Rx}$ is an antisense drug we designed to reduce apolipoprotein C-III, or apoC-III, protein production and lower triglycerides. ApoC-III regulates triglyceride metabolism in the blood and is an independent cardiovascular risk factor. People who do not produce apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease. ApoC-III is elevated in patients with dyslipidemia, or an abnormal concentration of lipids in the blood, and is frequently associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In human population studies, lower levels of apoC-III and triglycerides correlated with a lower rate of cardiovascular events. In certain populations, apoC-III mediates insulin resistance, which can make metabolic syndrome worse.

In preclinical studies, ISIS-APOCIII$_{Rx}$ diminished symptoms of metabolic syndrome and reduced atherosclerosis in mice. We have completed a Phase 1 study evaluating the safety and activity of ISIS-APOCIII$_{Rx}$ in healthy volunteers. In this study, ISIS-APOCIII$_{Rx}$ produced rapid, dose-dependent median reductions of up to 78 percent in apoC-III protein and up to 44 percent in blood triglycerides. All subjects tolerated ISIS-APOCIII$_{Rx}$ well.

We are pursuing a staged development plan for ISIS-APOCIII$_{Rx}$ designed to shorten the time to bring this drug to patients at high-risk of cardiovascular disease and pancreatitis. These are the patients with the highest unmet medical need who have severely high triglyceride levels despite currently available therapies and are at the greatest risk. Patients with triglycerides greater than 880 mg/dL are at a higher risk of developing pancreatitis, a painful and sometimes fatal disease that requires hospitalization and close monitoring. In these patients who cannot reduce their triglycerides to acceptable levels, the primary therapy is diet, which requires strict adherence and is often unsuccessful.

Our plan is to initially develop ISIS-APOCIII$_{Rx}$ to treat patients with triglyceride levels greater than 880 mg/dL and as we gain additional experience in these patients, expand to include other less severe patient populations. We are evaluating ISIS-APOCIII$_{Rx}$ in a Phase 2 study in patients with very high triglyceride levels of greater than 500 mg/dL. In this study, we plan to enroll approximately 100 patients who have triglyceride levels of 500 mg/dL or higher, and evaluate ISIS-APOCIII$_{Rx}$ as a monotherapy and in combination with fibrates. We are also evaluating ISIS-APOCIII$_{Rx}$ in patients with type 2 diabetes and high triglyceride levels. We plan to report Phase 2 data from these studies in 2013 or early 2014. We plan to initiate a Phase 3 program that will include evaluating ISIS-APOCIII$_{Rx}$ in patients with severely elevated triglyceride levels of greater than 880 mg/dL in late 2013 or early 2014.

ISIS-CRP$_{Rx}$ — ISIS-CRP$_{Rx}$ is an antisense drug that targets CRP, a protein produced in the liver. CRP levels increase dramatically during inflammatory disorders, and scientists have linked excessive amounts of CRP to coronary artery disease. Furthermore, a growing body of evidence from clinical trials implicates CRP in cardiovascular disease progression. These results suggest that it may be therapeutically beneficial to significantly decrease CRP levels in patients who are at risk for coronary events. In addition, clinicians have associated elevated CRP levels with a worsening of overall outcomes in conditions such as end-stage renal disease and multiple myeloma, suggesting that lowering CRP could help these patients. CRP elevation is also evident in many other major inflammatory diseases such as Crohn's disease and rheumatoid arthritis.

In preclinical studies, we observed that our antisense inhibitor of CRP suppressed liver and serum CRP levels. We evaluated ISIS-CRP$_{Rx}$ in a Phase 1 study in which ISIS-CRP$_{Rx}$ produced statistically significant reductions in CRP in the cohort of subjects that entered the study with elevated levels of CRP. All subjects tolerated ISIS-CRP$_{Rx}$ well. Our Phase 2 plan for ISIS-CRP$_{Rx}$ is to evaluate the drug in diseases with elevated CRP that could provide early proof-of-concept.

We completed a second Phase 1 study designed to evaluate if pretreatment with ISIS-CRP$_{Rx}$ can blunt an acute severe increase in CRP. In this study, healthy volunteers were treated with ISIS-CRP$_{Rx}$ and then subjected to an endotoxin challenge, which causes an increase in CRP and other inflammatory markers. We plan to report the data from this study in the first half of 2013. In addition, we are evaluating ISIS-CRP$_{Rx}$ in a Phase 2 study in patients with rheumatoid arthritis in which we will evaluate the effect of lowering CRP in patients with chronically elevated levels. We plan to report data from the Phase 2 rheumatoid arthritis study in 2013. We are also evaluating ISIS-CRP$_{Rx}$ in a Phase 2 study in patients with atrial fibrillation, or AF. AF involves an irregular heart rate that commonly causes poor blood flow to the body. In this study, we will evaluate the effect of lowering CRP on the frequency and duration of AF. We plan to report data from the AF study in early 2014.

ISIS-FXI$_{Rx}$ — ISIS-FXI$_{Rx}$ is an antisense drug we designed to treat clotting disorders. It targets Factor XI, a clotting factor produced in the liver that is an important component of the coagulation pathway. High levels of Factor XI increase the risk of thrombosis, a process involving aberrant blood clot formation responsible for most heart attacks and strokes. Elevated levels of Factor XI also increase the risk of venous thrombosis, a common problem after surgery, particularly major orthopedic procedures, such as knee or hip replacement. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Although currently available anticoagulants reduce the risk of thrombosis, physicians associate these anticoagulants with increased bleeding, which can be fatal.

In preclinical studies, ISIS-FXI$_{Rx}$ demonstrated potent antithrombotic activity with no increase in bleeding compared with standard anti-clotting agents, including low molecular weight heparin, warfarin and Factor Xa inhibitors, all of which increase bleeding. We have completed a Phase 1 study evaluating the safety and activity of ISIS-FXI$_{Rx}$ in healthy volunteers. In this study, ISIS-FXI$_{Rx}$ produced dose-dependent statistically significant reductions of greater than 80 percent in Factor XI protein. In this study, subjects tolerated ISIS-FXI$_{Rx}$ well with no increase in bleeding.

In 2012, we initiated a Phase 2 study evaluating ISIS-FXI$_{Rx}$ in patients undergoing knee replacement surgery, also referred to as total knee arthroplasty, or TKA. This study is a comparator-controlled study, in which we will compare the safety and activity of ISIS-FXI$_{Rx}$ to a commonly used anti-coagulant, enoxaparin. In this study, we are evaluating the effectiveness of ISIS-FXI$_{Rx}$ in reducing the number of thrombotic events in patients following TKA without increasing bleeding. Given the mechanism of Factor XI inhibition, we believe that doctors could use our drug broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic drugs are needed. We plan to report data from the Phase 2 study for ISIS-FXI$_{Rx}$ in 2013.

ISIS-APOA$_{Rx}$ — ISIS-APOA$_{Rx}$ is an antisense drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing Lp(a), an independent risk factor for cardiovascular disease. Scientists associate high levels of Lp(a) with an increased risk of atherosclerosis, coronary heart disease, heart attack and stroke. Commonly prescribed lipid-lowering drugs have little or no effect on Lp(a) levels. Even patients who can control their LDL-C levels remain at high-risk of cardiovascular events if they have high levels of Lp(a). There is a significant need for a highly specific drug that can lower Lp(a). We plan to develop ISIS-APOA$_{Rx}$ to treat patients with high Lp(a) levels who are at severe risk of experiencing cardiovascular events.

We plan to initiate a Phase 1 clinical study for ISIS-APOA$_{Rx}$ in 2013.

ISIS-FVII$_{Rx}$ — ISIS-FVII$_{Rx}$ is an antisense drug we designed to reduce Factor VII, a key component of the tissue factor coagulation pathway, for the treatment or prevention of thrombotic diseases. Clinicians have linked elevated levels of Factor VII activity with poor prognosis in several thrombotic diseases, such as heart attacks, and with cancer-associated thrombosis, which is the second leading cause of death in cancer patients.

In preclinical studies, antisense inhibition of Factor VII rapidly reduced Factor VII activity by more than 90 percent in three days, suggesting that physicians could use ISIS-FVII$_{Rx}$ in acute clinical settings, such as following surgery, to prevent patients from developing harmful blood clots. In addition, we observed no increase in bleeding with ISIS-FVII$_{Rx}$, which is a common side effect of currently available anti-thrombotic drugs. ISIS-FVII$_{Rx}$ is the second drug to enter development as part of our strategy to create more potent and safer anti-thrombotic drugs that do not increase bleeding.

We plan to complete preclinical studies to support an investigational new drug, or IND, application for ISIS-FVII$_{Rx}$ in 2013.

Severe & Rare Disease Franchise

Our severe and rare disease franchise is the largest franchise in our pipeline. We believe that our antisense technology could offer effective therapies for patients with severe and rare diseases that are life-threatening or fatal and for which there are limited treatment options. According to the National Institutes of Health, or NIH, there are approximately 5,000 to 8,000 rare diseases, many life-threatening or fatal. Unfortunately, patients with many of these severe and rare diseases have few effective therapies available. Since most severe and rare diseases are genetic or have a genetic component, parents often pass the disease to their children, creating a legacy of the disease and resulting in profound effects on the family.

We are discovering and developing antisense drugs to treat severe and rare diseases for which there is a need for new treatment options. Our partners, Biogen Idec and GSK, allow us to expand our drug discovery and development efforts beyond what we would choose to do internally. Due to the severe nature of these diseases and the lack of available treatments, there is an opportunity for more flexible and efficient development paths to the market. This means that, in some cases, the studies necessary for us to demonstrate proof-of-concept with a particular drug may also be the studies that complete our marketing registration package, thereby providing us with a relatively rapid path to market for potential new treatments for devastating and often fatal diseases.

Alicaforsen — Under license to Atlantic Pharmaceuticals Limited, alicaforsen is an antisense drug that targets intercellular adhesion molecule 1, or ICAM-1. ICAM-1 is over-expressed in a wide variety of inflammatory disorders, including ulcerative colitis and pouchitis. Ulcerative colitis, or UC, is an inflammatory bowel disease, or IBD, of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in UC patients who have had their diseased colons removed.

In 2007, we licensed alicaforsen to Atlantic Pharmaceuticals for pouchitis, UC and other inflammatory diseases. The FDA and EMA have since granted alicaforsen Orphan Drug Designation for the treatment of pouchitis in the United States and Europe, respectively. Atlantic Pharmaceuticals currently supplies alicaforsen in response to physicians' requests under international Named Patient Supply regulations for patients with pouchitis. We are eligible to receive royalties on product sales, including product sales under the Named Patient Supply from Atlantic Pharmaceuticals. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

KYNAMRO (mipomersen sodium) injection — Our flagship product, KYNAMRO, is on the market in the United States for patients with HoFH. For more information on KYNAMRO, see the previous KYNAMRO section, which is directly after the pipeline chart.

ISIS-TTR$_{Rx}$ — ISIS-TTR$_{Rx}$ is an antisense drug we designed to treat transthyretin amyloidosis, or TTR amyloidosis, a severe and rare genetic disease in which the patient inherits a mutant gene that produces a misfolded form of TTR, which progressively accumulates in tissues. In patients with TTR amyloidosis, both the mutant and normal forms of TTR can build up as fibrils in tissues, including heart, peripheral nerves, and the gastrointestinal tract. The presence of TTR fibrils interferes with the normal functions of these tissues, and as the TTR protein fibrils enlarge more tissue damage occurs and the disease worsens.

There are two common types of TTR amyloidosis, familial amyloid cardiomyopathy, or FAC, which affects more than 40,000 patients worldwide, and familial amyloid polyneuropathy, or FAP, which affects more than 10,000 patients worldwide. Patients with FAC have TTR build up in the heart muscle and succumb to heart failure approximately five to six years after symptom onset. Patients with FAP have TTR build up in peripheral nerve tissue leading to the loss of nerve function and wasting.

We designed ISIS-TTR$_{Rx}$ to inhibit the production of all forms of TTR, and to offer an alternative approach to treat all types of TTR-related amyloidosis. ISIS-TTR$_{Rx}$ is the first drug to enter development under our preferred partner alliance with GSK. In October 2012, we amended our agreement with GSK to reflect an accelerated development plan for ISIS-TTR$_{Rx}$. Under the terms of the original collaboration agreement with GSK, which includes six programs, we are eligible to receive on average up to $20 million in milestone payments per program before Phase 2 proof-of-concept plus a licensing fee, additional post-licensing milestone payments and double digit royalties on sales from each product. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, and received a $7.5 million milestone payment in February 2013 upon initiation of the ISIS-TTR$_{Rx}$ Phase 2/3 study. We have already received $17.5 million in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$, including the $7.5 million milestone payment we received in February 2013. We are also eligible to earn an additional $50 million in pre-licensing milestone payments to support the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, GSK has increased the regulatory and sales milestones payable to us should the product achieve registration and meet certain sales thresholds. We are also eligible to receive double-digit royalties on sales of ISIS-TTR$_{Rx}$.

We completed a Phase 1 study evaluating the safety and activity of ISIS-TTR$_{Rx}$ in healthy volunteers. In this study, ISIS-TTR$_{Rx}$ produced rapid, dose-dependent reductions in plasma TTR protein with many subjects achieving greater than 80 percent reduction in TTR protein and several subjects reaching TTR protein levels that were below the limit of assay detection at the highest doses. Subjects treated with ISIS-TTR$_{Rx}$ generally tolerated the drug well. In February 2013, we initiated a Phase 2/3 study to evaluate the efficacy of ISIS-TTR$_{Rx}$ in patients with FAP. In this study, we will enroll approximately 200 patients and evaluate the efficacy of ISIS-TTR$_{Rx}$ by measuring neurological dysfunction and quality of life in patients with FAP.

ISIS-SMN$_{Rx}$ — ISIS-SMN$_{Rx}$ is an antisense drug we designed to treat spinal muscular atrophy, or SMA, a severe motor-neuron disease that is the leading genetic cause of infant mortality. SMA affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. One in 50 people, approximately six million people in the United States, are carriers of the SMA gene. Carriers experience no symptoms and do not develop the disease. When both parents are carriers, however, there is a one in four chance that their child will have SMA. SMA is caused by a loss of, or defect in, the survival motor neuron 1, or *SMN1*, gene leading to a decrease in the protein survival motor neuron, or SMN. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. The severity of SMA correlates with the amount of SMN protein a person produces. Infants with Type I SMA, the most severe life-threatening form, produce very little SMN protein and have a shortened life expectancy. Children with Type II

and Type III SMA have greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA. The FDA granted Orphan Drug Designation with Fast Track Status to ISIS-SMN$_{Rx}$ for the treatment of patients with SMA.

We designed ISIS-SMN$_{Rx}$ to potentially treat all types of childhood SMA by altering the splicing of a closely related gene, *SMN2,* which leads to the increased production of fully functional SMN protein. Splicing is a normal cellular mechanism that the cell uses to produce many different, but closely related proteins from a single gene by varying the processing of the RNA. Splicing occurs on the precursor mRNA, or pre-mRNA, which includes sequences that encode for proteins and regions that are unnecessary for making proteins. The cell deletes the regions that are unnecessary for making proteins from the pre-mRNA strand before it produces the mRNA. Scientists call the natural process that removes these regions and re-forms the finished mRNA 'splicing'. Most of the diversity in proteins in the cell is due to splicing. In fact, of the approximately 25,000 genes in the human genome, approximately 90% have alternative splice forms. Alternative splicing can produce proteins that are involved in disease. In some cases like SMA, we are using antisense technology to direct alternate splicing to produce a deficient protein, SMN, critical for normal cellular function to correct for a genetic defect.

In January 2012, we and Biogen Idec entered into a preferred partner alliance that provides Biogen Idec an option to develop and commercialize ISIS-SMN$_{Rx}$. Under the agreement, we received an upfront fee and are responsible for developing ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. We will receive milestone payments from Biogen Idec as ISIS-SMN$_{Rx}$ advances through development. We are also eligible to receive double-digit royalties on sales of ISIS-SMN$_{Rx}$. We plan to initiate a Phase 2/3 program in 2013.

In December 2011, we initiated the first Phase 1 clinical study evaluating ISIS-SMN$_{Rx}$ in children with SMA. We designed the Phase 1 study of ISIS-SMN$_{Rx}$, a single-dose, dose-escalation study, to assess the safety, tolerability and pharmacokinetic profile of the drug in medically stable children with SMA between the ages of two and 14. In this study all patients have completed dosing and patients tolerated ISIS-SMN$_{Rx}$ well as a single dose administered directly into the cerebral spinal fluid. In this study, we also observed improvements in muscle function in a number of children. We plan to report the full data from this study at the American Academy of Neurology meeting in March 2013.

We initiated the Phase 1b/2a multiple-dose, dose-escalation study in October 2012 to evaluate the safety of multiple doses of ISIS-SMN$_{Rx}$ and to aid in identifying an appropriate dose to move into Phase 2/3 studies, which we are designing to support registration for marketing approval.

We acknowledge support from the following organizations for this program: Muscular Dystrophy Association, SMA Foundation, and Families of Spinal Muscular Atrophy. We have licensed intellectual property relating to this program from Cold Spring Harbor Laboratory and the University of Massachusetts Medical School.

ISIS-APOCIII$_{Rx}$ — ISIS-APOCIII$_{Rx}$ is an antisense drug we designed to reduce apolipoprotein C-III, or apoC-III, protein production and lower triglycerides. We are evaluating ISIS-APOCIII$_{Rx}$ for use in patients with severely elevated triglycerides of greater than 880 mg/dL. For more information on ISIS-APOCIII$_{Rx}$, please refer to the ISIS-APOCIII$_{Rx}$ section under the subheading "Cardiovascular Franchise."

ATL1103 — ATL1103 is an antisense drug that targets the growth hormone receptor, or GHr, a receptor that, when inhibited, reduces the level of circulating insulin-like growth factor-1, or IGF-1, produced in the liver. IGF-1 is a hormone that contributes to various diseases, including acromegaly, an abnormal growth disorder of organs, face, hands and feet. IGF-1 also contributes to diabetic retinopathy, a common disease of the eye and a leading cause of blindness, diabetic nephropathy of the kidney and certain forms of cancer. In preclinical studies, ATL1103 demonstrated significant reductions in IGF-1 levels in the blood and inhibition of neovascularization, or new blood vessels, in the eye in a mouse retinopathy model.

Antisense Therapeutics Limited, or ATL, is developing ATL1103. ATL has completed a Phase 1 study in healthy volunteers demonstrating that ATL1103 was safe and well tolerated. ATL is evaluating ATL1103 in a Phase 2 study in patients with acromegaly.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug that targets the glucocorticoid receptor, or GCCR. Glucocorticoid hormones affect a variety of processes throughout the body, and excessive levels of glucocorticoid hormones can have a detrimental effect on many of the tissues and organs in the body. Cushing's Syndrome is an orphan disease caused by prolonged exposure to high levels of glucocorticoids. If untreated, patients with Cushing's Syndrome can develop hypertension, diabetes and impaired immune functions and have an increased risk of early death. Although there are approved treatments for Cushing's Syndrome, current medicines are associated with significant side effects, such as hypertension and diabetes, and there remains a high unmet medical need for new therapies for these patients. We have already demonstrated that subjects tolerated ISIS-GCCR$_{Rx}$ well in a Phase 1 study in healthy volunteers, and we observed reductions of GCCR specifically in the liver and fat tissues, consistent with our preclinical observations. We plan to develop ISIS-GCCR$_{Rx}$ to treat patients with Cushing's Syndrome and, as explained later, to treat patients with type 2 diabetes who are also on metformin.

ISIS-AAT$_{Rx}$ — ISIS-AAT$_{Rx}$ is an antisense drug that reduces production of alpha-1 antitrypsin, or AAT, for the treatment of liver disease in patients with alpha-1 antitrypsin deficiency, or AATD. AATD is a genetic disease in which the patient does not produce normal AAT, a protein primarily produced in the liver that protects lung tissue from damage. AATD affects one out of every 2,500 people in the United States and can lead to severe liver disease, including liver scarring, cirrhosis and liver cancer.

Patients with AATD inherit a mutant gene from one or both parents. Physicians characterize patients who inherit a mutant gene from both parents as having severe AATD. Approximately 10 percent of infants and 15 percent of adults with severe AATD experience liver damage due to progressive accumulation of misfolded AAT protein in the liver. There are currently no available therapies for patients with AATD-associated liver disease, and liver transplantation is the only available option for patients who develop severe liver dysfunction due to accumulation of mutant AAT protein. Symptoms of AATD-associated liver disease can manifest as early as infancy, and AATD is the most common genetic disease requiring pediatric liver transplantation. The Alpha-1 Association estimates that approximately 10 to 15 percent of all liver transplant candidates have AATD.

ISIS-AAT$_{Rx}$ is the second drug to enter development under our preferred partner alliance with GSK. We are responsible for developing ISIS-AAT$_{Rx}$ through Phase 2 proof-of-concept, at which time GSK has the option to license ISIS-AAT$_{Rx}$ from us. We are eligible to receive milestone payments from GSK as ISIS-AAT$_{Rx}$ advances through development. We believe that ISIS-AAT$_{Rx}$ offers a unique approach to treat AATD-associated liver disease.

ISIS-PKK$_{Rx}$ — ISIS-PKK$_{Rx}$ is an antisense drug designed to prevent hereditary angioedema, or HAE, attacks. ISIS-PKK$_{Rx}$ inhibits the production of prekallikren, or PKK, a protein produced in the liver that plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea. HAE affects approximately 20,000 patients in the United States and Europe and can be fatal if swelling occurs in the larynx. In patients with frequent or severe attacks, doctors may use prophylactic treatment approaches to prevent and reduce the severity of HAE attacks. However, current prophylactic treatment approaches are very limited and have major tolerability issues due to challenging administration requirements leaving patients with few therapeutic options. By inhibiting the production of PKK, ISIS-PKK$_{Rx}$ could be an effective prophylactic approach to preventing HAE attacks. We plan to develop ISIS-PKK$_{Rx}$ as a once-weekly treatment to prevent HAE attacks in patients who are susceptible to acute and serious attacks.

Metabolic Franchise

Metabolic disorders are chronic diseases that affect millions of people. There is still a significant need for new therapies for these patients. According to the Centers for Disease Control and Prevention, diabetes affects more than 25 million people in the United States, or eight percent of the population, with type 2 diabetes constituting 90 to 95 percent of those cases.

Metabolic disease is a very large area of medical need and is another area in which we focus our drug discovery efforts. We now have three drugs in our pipeline to treat type 2 diabetes, each of which acts upon targets in the liver or fat tissue through a distinct mechanism to improve insulin sensitivity, reduce glucose production, or affect other metabolic aspects of this complex disease. We plan to keep building our metabolic disease franchise and we are expanding our focus beyond type 2 diabetes to obesity and nonalcoholic steatohepatitis, or NASH. NASH is a common and often asymptomatic liver disease that can cause irreversible damage to the liver, and lead to liver cirrhosis and cancer. There is a significant need to reduce liver fat in patients with metabolic disease because these patients can develop NASH if they accumulate too much fat in their liver.

Our approach is to develop antisense drugs that doctors can add to existing therapies to treat diabetes and obesity. One hurdle for traditional drug development is that most traditional drugs cannot selectively target a disease-causing protein without also affecting closely related proteins, which often results in unwanted side effects. We design our antisense drugs to target the gene responsible for producing the disease-causing protein while avoiding unwanted effects on closely related proteins, thereby reducing the risk of side effects. In addition, the liver and fat cells produce many of the most important therapeutic targets for metabolic disease, and our antisense drugs distribute to the liver and fat cells and inhibit the production of key therapeutic targets in these organs.

ISIS-PTP1B$_{Rx}$ — ISIS-PTP1B$_{Rx}$ is an antisense drug that targets protein tyrosine phosphatase-1B, or PTP-1B, to treat type 2 diabetes. PTP-1B is a phosphatase that negatively regulates insulin receptor signaling and is responsible for turning off the activated insulin receptor. Reducing PTP-1B enhances insulin activity. Scientists have long recognized PTP-1B as an attractive target to treat diabetes, but due to structural similarities among closely related proteins, pharmaceutical companies have had difficulty identifying small molecule drugs with sufficient specificity to be safe. We designed ISIS-PTP1B$_{Rx}$ to increase the body's sensitivity to the natural hormone insulin, resulting in better glucose control for patients with type 2 diabetes. Because of its unique mechanism, ISIS-PTP1B$_{Rx}$ may help treat type 2 diabetes without causing weight gain or hypoglycemia, also known as low blood sugar. The reductions in LDL-C produced by inhibiting PTP-1B should also provide an added benefit to patients.

Phase 2 studies of ISIS 113715, our previous PTP-1B inhibitor, showed that inhibiting PTP-1B could help patients with type 2 diabetes. In those studies, inhibiting PTP-1B improved glucose control and reduced LDL-C in both newly diagnosed diabetic patients and in patients who were taking sulfonylureas. The patients in these studies also did not gain weight, indicating another substantial advantage in treating diabetic patients who are frequently obese and at high cardiovascular risk.

We have completed a Phase 1 study evaluating the safety of ISIS-PTP1B$_{Rx}$ in healthy volunteers. In this study, subjects tolerated ISIS-PTP1B$_{Rx}$ well. We also observed encouraging data in measures of insulin sensitivity and in a biomarker associated with weight loss. These Phase 1 data are consistent with our findings from our Phase 2 ISIS 113715 studies and support our preclinical observations of increased potency with ISIS-PTP1B$_{Rx}$ compared to ISIS 113715.

We believe that physicians may use ISIS-PTP1B$_{Rx}$ in combination with most of the other commonly used drugs, including insulin, GLP-1 agonists, and more traditional drugs like metformin, to treat patients with diabetes. The clinical development plan for ISIS-PTP1B$_{Rx}$ focuses on treating diabetic patients who are inadequately controlled on insulin, helping them utilize insulin more efficiently and treating patients who are beginning to fail oral therapies, extending the time they have before becoming dependent on insulin. In 2013, we plan to initiate a Phase 2 study in patients with type 2 diabetes who despite taking metformin have uncontrolled glucose levels.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug that targets GCCR. Glucocorticoid hormones effect a variety of processes throughout the body, including promoting liver glucose production and fat storage. Scientists associate excessive GCCR activity in the liver and fat with obesity, insulin resistance and glucose intolerance. Although scientists have long recognized inhibiting GCCR as an attractive strategy for improving glycemic and lipid control in patients with type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged traditional drug developers. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to inhibit glucocortocoid action primarily in liver and fat tissue. Notably, antisense drugs delivered systemically do not reduce GCCR expression in the central nervous system or adrenal glands, which could lead to systemic side effects. Reducing GCCR specifically in the liver and fat tissues is an attractive therapeutic approach because it lowers glucose and lipids, without causing potential side effects associated with systemic GCCR inhibition.

In preclinical studies, we showed that we can reduce GCCR specifically in the liver and fat tissues. In addition, we have shown that antisense inhibition of GCCR produced robust lowering of blood glucose, lipid levels and decreased body fat in obese animals. We have completed a Phase 1 study evaluating the safety of ISIS-GCCR$_{Rx}$ in healthy volunteers. In this study, subjects tolerated ISIS-GCCR$_{Rx}$ well, and we observed reductions of GCCR specifically in the liver and fat tissues, consistent with our preclinical observations.

We believe that doctors could use ISIS-GCCR$_{Rx}$ in diabetic patients with moderate to severe hyperglycemia who are also obese or have high levels of cholesterol and triglycerides. We also believe that there are other attractive therapeutic opportunities for doctors to use ISIS-GCCR$_{Rx}$ in patients with diseases in which there is glucocorticoid excess, such as Cushing's Syndrome, and other diseases where a selective GCCR inhibitor could be beneficial. We

plan to develop ISIS-GCCR$_{Rx}$ to treat patients with Cushing's Syndrome. However, our initial focus is in patients with type 2 diabetes, and we plan to initiate a Phase 2 study in 2013 to evaluate ISIS-GCCR$_{Rx}$ in patients with type 2 diabetes who are also on metformin.

ISIS-GCGR$_{Rx}$ — ISIS-GCGR$_{Rx}$ is an antisense drug that targets the glucagon receptor, or GCGR, to reduce the effects of glucagon. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose, particularly in type 2 diabetes. In patients with advanced diabetes, uncontrolled glucagon action leads to a significant increase in blood glucose levels. Therefore, attenuating glucagon action could have a significant glucose lowering effect in patients with severe diabetes. In addition, reducing GCGR produces more active glucagon-like peptide, or GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion. Therefore, we believe we can help control type 2 diabetes by using an antisense drug to reduce GCGR, which will stop the liver from producing too much glucose while preserving pancreatic function.

We conducted preclinical studies in the most insulin-resistant models of type 2 diabetes. In these studies, antisense reduction of GCGR decreased excessive liver glucagon action, produced robust glucose control, reduced levels of triglycerides and helped preserve the pancreas without producing hypoglycemia. Although researchers have developed and evaluated small molecule inhibitors of GCGR and observed glucose-lowering effects, treatment with these small molecule inhibitors also produced side effects limiting their potential use as drugs, including increases in lipids and blood pressure. We have completed a Phase 1 study evaluating the safety of ISIS-GCGR$_{Rx}$ in healthy volunteers. In this study, subjects tolerated ISIS-GCGR$_{Rx}$ well with no clinically significant increases in lipids or blood pressure and with no hypoglycemia. In addition, we observed an increase in active GLP-1, which was consistent with our preclinical observations.

Given the unique mechanism of action and potentially favorable safety profile observed in the Phase 1 study, we believe that doctors could use ISIS-GCGR$_{Rx}$ in diabetic patients with severe hyperglycemia who are not controlled with current treatments and who could benefit from a drug that significantly decreases glucose levels and preserves pancreatic function. We plan to initiate a Phase 2 study in 2013 to evaluate ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes who despite taking metformin have uncontrolled glucose levels.

ISIS-FGFR4$_{Rx}$ — ISIS-FGFR4$_{Rx}$ is an antisense drug that specifically reduces the production of fibroblast growth factor receptor 4, or FGFR4, in the liver and fat tissues, which decreases the body's ability to store fat while simultaneously increasing fat burning and energy expenditure. Many anti-obesity drugs act in the brain to suppress appetite, commonly resulting in CNS side effects. However, ISIS-FGFR4$_{Rx}$ does not distribute to the brain or CNS and therefore should not produce any CNS side effects.

In preclinical studies, antisense inhibition of FGFR4 lowered body weight when we administered it as a single agent and in the presence or absence of a calorie-restricted diet. Additionally, inhibiting FGFR4 decreased body weight when we administered it in combination with an appetite-suppressing drug. In addition to reducing body weight, inhibiting FGFR4 demonstrated an improvement in insulin sensitivity. ISIS-FGFR4$_{Rx}$ is the first drug in our metabolic franchise to treat obesity and utilizes technology we in-licensed from Verva Pharmaceuticals Ltd.

We plan to report data from a Phase 1study for ISIS-FGFR4$_{Rx}$ in healthy subjects in 2013.

ISIS-DGAT2$_{Rx}$ — ISIS-DGAT2$_{Rx}$ is an antisense drug that specifically reduces the production of diacylglycerol acyltransferase-2, or DGAT-2, a key component in the synthesis of triglycerides. By reducing DGAT2, ISIS-DGAT2$_{Rx}$ should reduce liver fat in patients with NASH. The NIH estimates that NASH affects more than 20 million people in the United States and expects the number to increase as the rate of obesity rises. There are no effective therapies available for patients with NASH and current treatments consist only of lifestyle changes. In addition, because clinicians associate increases in liver fat with insulin resistance, ISIS-DGAT2$_{Rx}$ could also benefit patients with type 2 diabetes who are insulin resistant.

Cancer Franchise

We are discovering and developing antisense drugs to treat cancers both internally and through our partnerships with AstraZeneca and OncoGenex Technologies Inc. Cancer is an area of significant unmet medical need and an area in which our antisense technology provides us with unique advantages in discovering new drugs. Cancer is an extremely complex disease that involves a large number of targets. With our technology we can evaluate a very broad and diverse range of targets and identify their involvement in different types of cancers. Using the information we gain early in research on each of these targets, we can quickly identify the most promising targets for an anti-cancer drug. We select anti-cancer targets that provide a multi-faceted approach to treating cancer.

Our cancer pipeline consists of anti-cancer antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. In 2012, we formed an anti-cancer alliance with AstraZeneca that supports our efforts to expand our anti-cancer efforts and supports an aggressive and broad clinical development plan for ISIS-STAT3$_{Rx}$. AstraZeneca brings significant experience and broad collaborations that enable the identification of novel genetic and epigenetic targets for cancer. Combining AstraZeneca's expertise with our drug discovery technology, we plan to expand our cancer franchise with a number of promising new anti-cancer targets.

We believe the favorable tolerability and early evidence of clinical benefit of the anti-cancer drugs in our pipeline demonstrate how uniquely suited our technology is to create novel cancer therapeutics. In addition, we believe our generation 2.5 chemistry enhances the potency and effectiveness of our antisense drugs, and extends the applicability of our technology to cancers that are difficult to treat. For instance, we presented positive interim Phase 1 data on our generation 2.5 drug, ISIS-STAT3$_{Rx}$, in patients with advanced cancer who were refractory to prior chemotherapy treatment. In this interim analysis, we observed clear responses in these patients with an acceptable safety profile. Based on these data, we and AstraZeneca are currently evaluating ISIS-STAT3$_{Rx}$ in a clinical study in focused patient populations with advanced cancer.

Custirsen — Custirsen, formerly OGX-011, now under license to Teva Pharmaceutical Industries Ltd., or Teva, is a second-generation antisense drug that targets clusterin, a secreted protein that acts as a cell-survival protein and is over-expressed in response to anti-cancer agents. We and OncoGenex jointly discovered and conducted the initial development of custirsen. In December 2009, OncoGenex licensed custirsen to Teva as part of a global license and collaboration agreement to develop and commercialize custirsen. Teva and OncoGenex are studying custirsen for use as an adjunct therapy to enhance the effectiveness of chemotherapy. Custirsen has shown promising results in combination with currently available chemotherapies in several tumor types. The FDA granted Fast Track Designation to custirsen for the treatment of metastatic prostate cancer in combination with docetaxel. OncoGenex has stated that the FDA has also agreed on the design of the SYNERGY trial, a Phase 3 trial evaluating custirsen, via the SPA process.

OncoGenex and collaborating investigators evaluated custirsen in five Phase 2 studies in combination with various cancer therapies for prostate cancer, non-small cell lung cancer, or NSCLC, and breast cancer. OncoGenex reported results from a randomized Phase 2 study of custirsen in patients with advanced metastatic castrate resistant prostate cancer, or CRPC. In this study, OncoGenex reported a median overall survival of 23.8 months in patients treated with custirsen plus docetaxel compared to 16.9 months for patients treated with docetaxel alone. In addition, OncoGenex reported that the unadjusted hazard ratio, a measure used to determine the difference in survival between treatment groups, was 0.61, representing a 39 percent reduction in the rate of death for patients treated with custirsen. OncoGenex also reported that patients treated with custirsen in combination with docetaxel tolerated custirsen well.

OncoGenex has also evaluated custirsen in a Phase 1/2 combination study in patients with NSCLC. In January 2012, OncoGenex reported that one- and two-year survival rates were 54 percent and 30 percent, respectively, and 12 percent of patients were still alive at a median follow-up of 41 months. The median overall survival was 14.1 months and progression-free survival was 4.3 months.

Teva and OncoGenex are collaborating on a global Phase 3 clinical program in patients with metastatic CRPC and metastatic NSCLC. OncoGenex and Teva are evaluating custirsen in two Phase 3 clinical studies for first- and second-line chemotherapy in patients with metastatic CRPC. OncoGenex and Teva are also evaluating custirsen in a Phase 3 study as a second-line treatment in patients with NSCLC. Teva and OncoGenex have completed enrollment for the SYNERGY study as a first-line treatment in patients with CRPC and expect results for the survival primary endpoint in the fourth quarter of 2013.

ISIS-EIF4E$_{Rx}$ — ISIS-EIF4E$_{Rx}$ targets the gene that is responsible for producing the protein eukaryotic initiation factor-4e, or eIF-4E, which cells over-express in a variety of cancers, including prostate, lung, ovarian, liver, breast, head and neck, bladder, colon, thyroid and lymphoma. eIF-4E facilitates the synthesis of factors in the body that support the development, growth, progression and survival of cancer. In preclinical studies, we and collaborators demonstrated marked anti-cancer activity in a broad range of animal models of cancer and provided the first in vivo evidence that tumor growth may be more susceptible to eIF-4E inhibition than growth of normal tissue. Targeting eIF-4E has been of great interest to the pharmaceutical industry and the oncology community. However the pharmaceutical industry considers eIF-4E a difficult protein to target with traditional pharmaceutical approaches.

Eli Lilly and Company completed a Phase 1 study of ISIS-EIF4E$_{Rx}$ in patients with cancer that showed that the subjects tolerated the drug well at doses up to 1200 mg per week. Eli Lilly and Company has rights to license ISIS-EIF4E$_{Rx}$ from us on predefined terms.

In 2010, we initiated a Phase 2 program of ISIS-EIF4E$_{Rx}$ in patients with NSCLC and prostate cancer. The endpoints for both studies include progression-free survival, overall survival, response rates, time to progression and the reduction of a variety of biomarkers. We plan to report data from the Phase 2 program in 2013.

OGX-427 — OGX-427 is a second-generation antisense drug targeting heat shock protein 27, or Hsp27, which is a cell survival protein that cells over-produce in response to many cancer treatments, including hormone ablation therapy, chemotherapy and radiation therapy. Studies have shown that increased Hsp27 production is prevalent in many human cancers, including prostate, NSCLC, breast, ovarian, bladder, renal, pancreatic, multiple myeloma and liver cancers. Studies have also linked increased Hsp27 production to faster rates of cancer progression, treatment resistance and shorter survival duration.

OncoGenex is evaluating OGX-427 in patients with cancer. In June 2010, OncoGenex reported results from a Phase 1 study of OGX-427 in patients with a variety of cancers. In this study, patients treated with OGX-427 as a monotherapy and in combination with docetaxel tolerated the drug well. In addition, OGX-427, when used as a single agent, demonstrated declines in circulating tumor cells at all doses and in all types of cancer OncoGenex evaluated. OGX-427 also demonstrated evidence of reduction in tumor markers defined as declines of prostate-specific antigen, or PSA, levels in prostate cancer and cancer-antigen-125 levels in ovarian cancer.

In February 2012, OncoGenex reported preliminary results from a Phase 1 study in patients with superficial bladder cancer. In this study, OncoGenex reported that treatment with OGX-427 resulted in a trend towards decreased levels of Hsp27 and increased tumor cell death rates.

OncoGenex is also evaluating OGX-427 in a Phase 2 study for the first-line treatment of metastatic bladder cancer and in two Phase 2 studies for the treatment of metastatic CRPC. In September 2012, OncoGenex reported preliminary results from a Phase 2 study in patients with CRPC. In this study, OncoGenex reported that treatment with OGX-427 in combination with prednisone resulted in a higher number of patients without disease progression at 12 weeks and greater declines in prostate-specific antigen, or PSA, and circulating tumor cells compared to patients treated with prednisone alone.

ISIS-STAT3$_{Rx}$ — We designed ISIS-STAT3$_{Rx}$ to treat cancer by inhibiting the production of a gene critical for tumor cell growth and survival. Signal transducer and activator of transcription 3, or STAT3, is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma and promotes tumor cell growth and prevents cell death.

In 2012, we licensed ISIS-STAT3$_{Rx}$ to AstraZeneca as part of a broad alliance to discover and develop anti-cancer drugs. We are eligible to receive up to $75 million in milestone payments over the next two years, including up to a $50 million milestone payment subject to meeting pre-agreed efficacy and safety criteria in the ongoing ISIS-STAT3$_{Rx}$ study. We are also eligible to receive double-digit royalties on sales of ISIS-STAT3$_{Rx}$.

ISIS-STAT3$_{Rx}$ is our first drug to incorporate our new generation 2.5 chemistry. We believe the significant potency we observed in our preclinical studies with ISIS-STAT3$_{Rx}$ broadens the therapeutic opportunities for ISIS-STAT3$_{Rx}$ into many different types of cancer where STAT3 is implicated. Our initial focus is to evaluate ISIS-STAT3$_{Rx}$ in hematologic malignancies, such as lymphoma. Together with AstraZeneca, we have designed a development plan that could allow for a rapid path to the market in these patient populations. In parallel, AstraZeneca is planning to initiate a broad Phase 2 program for ISIS-STAT3$_{Rx}$ with additional clinical studies in 2013 or early 2014.

In preclinical studies, ISIS-STAT3$_{Rx}$ demonstrated antitumor activity in animal models of human cancer with an attractive safety profile. In 2012, we reported interim Phase 1 data in patients with cancer who were refractory to prior chemotherapy treatment. In this study, we showed that ISIS-STAT3$_{Rx}$ treatment resulted in clear responses in patients with advanced cancer with an acceptable safety profile. Based on this data, we initiated a Phase 2 study in focused patient populations with advanced cancer.

ISIS-AZ1$_{Rx}$ — ISIS-AZ1$_{Rx}$ is an antisense drug to an undisclosed target designed to treat cancer. ISIS-AZ1$_{Rx}$ is a generation 2.5 drug and the first drug to arise from a research program and enter development under our partnership with AstraZeneca. We granted AstraZeneca an exclusive license to develop and commercialize ISIS-AZ1$_{Rx}$. We are responsible for developing ISIS-AZ1$_{Rx}$ through completion of IND-enabling toxicology and will receive milestone payments from AstraZeneca as ISIS-AZ1$_{Rx}$ advances in development. We are also eligible to receive double-digit royalties on sales of ISIS-AZ1$_{Rx}$. We plan to initiate preclinical studies to support an investigational new drug application for ISIS-AZ1$_{Rx}$ in 2013.

Other Drugs in Development

The broad applicability of our antisense technology allows us to create promising drugs in a variety of disease areas. We have successfully developed novel drugs designed to treat many different diseases. In therapeutic areas that are outside of our core areas of development, we license our drugs to highly focused satellite companies that have the specific expertise and resources to continue developing the drugs. Together with our partners we continue to advance drugs in clinical development that are outside of our core therapeutic areas. For instance, our partner, Excaliard, presented data from three Phase 2 studies demonstrating that EXC 001 reduced scarring in patients.

ISIS-CRP$_{Rx}$ — ISIS-CRP$_{Rx}$ is an antisense drug that targets CRP, a protein produced in the liver. CRP levels increase dramatically during inflammatory disorders, including rheumatoid arthritis. We are evaluating ISIS-CRP$_{Rx}$ in patients with rheumatoid arthritis. For more information on ISIS-CRP$_{Rx}$, please refer to the ISIS-CRP$_{Rx}$ section under the subheading “Cardiovascular Franchise”.

ATL1102 — ATL1102 is an antisense drug that ATL is developing for the treatment of multiple sclerosis, or MS. ATL1102 inhibits CD49d, a subunit of Very Late Antigen-4, or VLA-4. Studies in animal models have demonstrated that inhibiting VLA-4 positively affects a number of inflammatory diseases, including MS. We licensed ATL1102 to ATL in December 2001 and in February 2008, ATL licensed ATL1102 to Teva . In 2008, ATL and Teva reported Phase 2a results of ATL1102 showing significantly reduced disease activity in patients with relapsing remitting MS. In 2010, Teva terminated its agreement with ATL and returned ATL1102 back to ATL. ATL is seeking a partner to continue developing ATL1102 in patients with MS.

EXC 001 — EXC 001 is an antisense drug that targets connective tissue growth factor, or CTGF, a growth factor that is over-expressed in damaged skin or tissue following a traumatic event. We co-discovered EXC 001 and licensed it to Excaliard for the local treatment of fibrotic diseases, including scarring. Fibrosis represents a significant and expanding area of unmet medical need where antisense drugs could offer a unique advantage as anti-fibrotic agents. In November 2011, Pfizer Inc. acquired Excaliard.

iCo-007 — iCo-007 is an antisense drug that targets c-Raf kinase. In preclinical studies, clinicians associated antisense inhibition of c-Raf kinase with a reduction in the formation and leakage of new blood vessels in the eye, suggesting inhibiting c-Raf kinase can help patients with diabetic macular edema and diabetic retinopathy. Diabetic retinopathy is one of the leading causes of blindness in people in the United States, and a high percentage of type 1 diabetics have evidence of retinopathy by age 20. Additionally up to 21 percent of people with type 2 diabetes have retinopathy at the time of the first diagnosis of diabetes, and most will eventually develop some degree of retinopathy over time. We discovered iCo-007 and licensed it to iCo Therapeutics Inc., or iCo, for the treatment of various eye diseases that occur as complications of diabetes.

In May 2010, investigators evaluating iCo-007 in patients with diffuse diabetic macular edema presented positive results from the Phase 1 study showing that subjects tolerated iCo-007 well. In this study, a number of individuals exhibited a decrease of central macular edema compared to baseline using an analytical method called optical coherence tomography. iCo is currently evaluating iCo-007 in a Phase 2 study in patients with diabetic macular edema and plans to report data in 2013.

Plazomicin —Plazomicin, formerly ACHN-490, is a next-generation aminoglycoside drug that Achaogen, Inc. is developing for the treatment of multi-drug resistant gram-negative bacterial infections. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. Achaogen discovered plazomicin based on technology licensed from us.

Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli, and against methicillin-resistant staphylococcus aureus, or MRSA. In preclinical studies, plazomicin demonstrated an acceptable safety profile and the potential for once-daily dosing. Achaogen has completed a Phase 1 study of plazomicin in healthy volunteers and a Phase 2 study. In the Phase 2 study, Achaogen evaluated plazomicin compared to levofloxacin for the treatment of complicated urinary tract infections and acute kidney infections in adults. In this study, patients treated with plazomicin tolerated the drug well and patients demonstrated favorable activity of plazomicin as compared to levofloxacin. Achaogen plans to initiate the next clinical study in 2013, which they designed to evaluate plazomicin’s effectiveness in treating seriously ill patients for whom currently available therapies are ineffective.

XEN701 — XEN701 is an antisense drug designed to treat anemia of inflammation, or AI. Anemia is a condition in which the body has a lower than normal number of red blood cells. AI is a type of anemia that commonly occurs with chronic, or long-term illnesses, including cancer and inflammatory disorders. Patients with AI cannot use iron properly, which results in a reduction of red blood cell production. XEN701 targets a hormone secreted by the liver in response to inflammatory mediators that inhibits intestinal iron uptake and release of stored iron.

XEN701is the first drug to enter development in our collaboration with Xenon Pharmaceuticals to develop antisense drugs that target the hepcidin-hemojuvelin pathway to treat AI. Antisense drugs targeting hemojuvelin and hepcidin should provide therapeutic benefit to patients with AI by reversing iron disturbances and facilitating red blood cell production.

ISIS-GSK3$_{Rx}$ — ISIS-GSK3$_{Rx}$ is an antisense drug to an undisclosed target designed to treat a viral infection. ISIS-GSK3$_{Rx}$ is the third drug to enter development under our collaboration with GSK. We will receive milestone payments from GSK as ISIS-GSK3$_{Rx}$ advances in development, and we are responsible for development of the drug up to phase 2 proof-of-concept, at which time GSK has the option to license ISIS-GSK3$_{Rx}$ from us. We are also eligible to receive double-digit royalties on sales of ISIS-GSK3$_{Rx}$. We plan to initiate preclinical studies to support an investigational new drug application for ISIS-GSK3$_{Rx}$ in 2013.

Antisense Technology

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. We can design our antisense drugs to target a broad range of diseases, efficiently producing a proprietary portfolio of drugs that can interrupt the production of disease-causing proteins without disrupting other proteins that are necessary for the body's normal functions. We are currently pursuing antisense drug discovery programs focused on various cardiovascular, severe and rare, neurologic and metabolic diseases and cancer.

Genes contain the information necessary to produce proteins. A gene is made up of nucleoside bases: Adenine, Thymine, Guanine, and Cytosine, commonly known as A, T, G and C, which are linked together to form a two-stranded structure that resembles a twisted ladder, known as deoxyribonucleic acid, or DNA. The nucleotides on one side of the ladder bind weakly to complementary nucleotides on the other strand according to specific rules; for example, A pairs with T and G pairs with C, creating the ladder's rungs. Scientists call this highly specific nucleotide pairing hybridization. The sequence or order of these nucleotides establishes the cell's recipes for making proteins. Each protein's instructions reside in a corresponding segment of DNA known as a gene.

When a cell transcribes information from a DNA gene into messenger RNA, or mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template and information stored in the DNA strand is copied into a complementary mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in doing so, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the synthesis of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the 'sense' strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Specifically, almost all of our antisense drugs in development cause a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target mRNA. The drug itself remains intact during this process, so it can remain active against additional target mRNA molecules and repeatedly trigger their degradation. Our antisense drugs can selectively bind to an mRNA that codes for a specific protein and will not bind to closely related RNAs, providing a level of specificity that is better than traditional drugs. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique specificity means that antisense drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets.

Further, the design of antisense compounds is less complex, more rapid and more efficient than traditional drug discovery approaches directed at protein targets. Traditional drug design requires companies to identify a small molecule that will interact with protein structures to affect the disease-causing process. Since predicting which small molecules will do this has proven to be difficult, traditional drug discovery involves testing hundreds of thousands of small molecules for their ability to interfere with protein function. As a result, traditional drug discovery is a labor intensive, low probability endeavor. In contrast, we design our antisense compounds to bind to mRNA through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the target mRNA.

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. This efficiency represents a unique advantage of our antisense drug discovery process. Antisense core technology is the function within Isis that is responsible for advancing antisense technology. Through the efforts of our scientists in the antisense core technology group, we have produced second generation antisense drugs that have increased potency and stability. In recent years, our scientists have improved the screening assays for our drugs, which led to the discovery of second generation antisense drugs that have demonstrated enhanced tolerability profiles in early clinical studies. For example, our drugs ISIS-TTR_{Rx} and ISIS-FXI_{Rx} are drugs we discovered through our improved screening assays. In Phase 1 studies evaluating these drugs in healthy volunteers, subjects reported approximately 65 percent fewer injection site reactions and no flu-like symptoms compared to subjects treated with KYNAMRO, an earlier second generation drug.

We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drugs. The goal of our target-based research programs is to identify antisense drugs to treat diseases for which there are large commercial markets or for which there is a need for better drugs. In addition, our research programs focus on the planned advancement of our technology for future antisense drugs. In 2010, we selected our generation 2.5 chemistry, an advancement that we believe will increase the potency of our drugs and make oral administration commercially feasible. We expect that these generation 2.5 drugs will constitute some of our future drugs and serve as follow-on compounds to some of our current drugs in development. Currently our ISIS-$STAT3_{Rx}$, ISIS-$FVII_{Rx}$, and ISIS-$AZ1_{Rx}$ drugs incorporate our generation 2.5 chemistry.

Other Antisense Targets and Mechanisms

There are more than a dozen antisense mechanisms that can be exploited with our antisense technology. While the majority of the drugs in our pipeline bind to mRNAs and inhibit the production of disease-causing proteins through the RNase H mechanism, we believe that our antisense technology is broadly applicable to many different antisense mechanisms, including RNAi and splicing, and many different RNA targets, including non-coding RNAs and toxic RNAs. For example, RNAi is an antisense mechanism that uses small interfering RNA, or siRNA, that exploit a cellular protein complex called the RNA-induced silencing complex, or RISC, to bind to the mRNA and to prevent the production of a disease-causing protein. Most companies approach siRNA using double-stranded oligonucleotides, which due to their properties require complex formulations to achieve delivery. We have created single-stranded RNAi compounds that, when we administer systemically, distribute in a manner similar to our second-generation RNase H antisense drugs, without requiring the complex formulation or delivery vehicle typically necessary for double-stranded RNAi oligonucleotides. These new single-stranded RNAi drug designs are an exciting advancement in RNAi technology. In 2012, we published two papers in the journal Cell demonstrating that single-stranded RNAi drugs distributed broadly, activated the RNAi pathway and reduced expression of targeted genes in animal models. These data provide compelling evidence that single-stranded oligonucleotides can be designed to exploit the RNAi pathway and silence gene expression of specific mRNAs in target tissues.

In addition, the diversity of our technology provides us with the potential to utilize many different antisense approaches, like alternative splicing. Because splicing occurs at the RNA level, we can utilize our technology to direct splicing to produce a particular protein product. For example, SMA is a splicing disorder caused by a loss of, or defect in, the survival motor neuron 1, or *SMN1,* gene leading to a decrease in the protein, survival motor neuron, or SMN. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. We designed our ISIS-SMN_{Rx} drug to alter the splicing of a similar gene, *SMN2,* to increase production of a fully functional SMN protein. ISIS-SMN_{Rx} is currently being

evaluated in a Phase 2 study in children with SMA. There are a number of diseases that scientists believe are splicing disorders. These are diseases we could potentially treat using antisense modulation of splicing and include cystic fibrosis and Duchenne's muscular dystrophy.

Because there are many different types of RNA that exist within the body, our antisense technology is not limited to RNA sequences that translate into proteins, but rather we can apply the principles of our technology to develop drugs that target other non-coding RNAs, such as microRNAs. To date, scientists have identified more than 700 microRNAs in the human genome, and have shown that the absence or presence of specific microRNAs in various cells is associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. MicroRNAs themselves may be drug targets. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-based therapeutics.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a development pipeline of 28 drugs, to create a broad base of potential license fees, milestone payments, royalties, profit sharing and earn out payments and to control our drug development expenses. In this way, we remain a focused and efficient research and development organization that can continue to discover new drugs and expand ours and our partners' pipelines.

Through the efficiency of our drug discovery platform we can develop drugs to almost any gene target. We concentrate on developing antisense drugs in our core therapeutic areas of cardiovascular, severe and rare, neurologic and metabolic diseases and cancer. To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner early in the development of a drug. In this way, we benefit in the short term from upfront fees and development milestone payments while we maintain control over the early development of the drug. We benefit in the long term by having a knowledgeable and committed partner to license the drug at clinical proof-of-value and by receiving regulatory milestone payments and royalties as our partner moves the drug to the market. We also work with a consortium of smaller companies that can exploit our drugs and technologies outside our primary areas of focus. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company drug development partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. Through this strategy we can expand the therapeutic range of antisense drugs into diseases that need new and innovative treatment options.

In addition, we form partnerships focused on developing and advancing certain RNA-targeting therapeutic technologies. These partnerships take advantage of our dominant intellectual property estate, and leverage our investments in our core technologies. These collaborations typically involve a cross-license between us and our partner and allow us to participate in newly emerging approaches to RNA-targeting therapeutics and augment our active programs in these areas.

Our partnerships fall into several categories, including pharmaceutical alliances and licenses, satellite company collaborators, external project funding alliances, and technology and intellectual property sales and licensing. We discuss each of these categories in more detail below, along with the relevant partnerships.

Pharmaceutical Alliances and Licensing

We have a strong history of establishing alliances with pharmaceutical industry leaders. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, and build a broad base of license fees, milestone payments and royalty income. In addition, we form preferred partner transactions that provide us with a vested partner early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like rare diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. This strategy allows us to benefit in the short term from upfront fees and milestone payments while reducing our risk and avoiding the cost of later-stage clinical studies. We also maintain control over the early development of the drug. We benefit in the long term by having a knowledgeable and committed partner to license the drug at clinical proof-of-value and by receiving regulatory milestone payments and royalties as our partner moves the drug to the market. We also form preferred partner transactions that allow us to expand and broaden our drug discovery efforts to new disease targets in therapeutic areas that are outside of our expertise or in areas where our partners will provide tools and resources that will complement our drug discovery efforts. For instance, we are working with our partner, AstraZeneca, to conduct a comprehensive clinical program for ISIS-STAT3$_{Rx}$, an anti-cancer drug we licensed to AstraZeneca. Through our collaboration, we are also applying AstraZeneca's proprietary preclinical cancer models and screening systems to evaluate new oncology targets.

In all of our partnerships, we benefit from the expertise our partners bring to our drugs. By coupling our partnering activity with our efficient drug discovery technology we can develop the majority of our drugs in our core therapeutic areas through early proof-of-value ourselves prior to licensing. As a result of our unique strategy and innovative research and development capabilities, we can keep our organization small and focused.

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca valued at up to $1 billion to discover and develop antisense drugs against five cancer targets. The agreement includes $31 million in upfront and near-term payments, comprising a $25 million payment we received in December 2012 and a $6 million payment we are eligible to receive in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees and double-digit royalties on any product sales of drugs resulting from this collaboration. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ for the treatment of cancer and a preclinical program, ISIS-AZ1$_{Rx}$, and an option to license up to three drugs we expect to develop under a separate research program.

We are currently conducting a focused clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced cancer. We are responsible for completing the ongoing clinical study and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. We have the potential to receive up to $75 million in milestone payments over the next two years, including the potential to receive up to a $50 million milestone payment subject to meeting pre-agreed efficacy and safety criteria in the ongoing ISIS-STAT3$_{Rx}$ study. If AstraZeneca successfully develops drugs under all three programs, we could receive substantive milestone payments of more than $980 million, including up to $325.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We will earn the next milestone payment of $10 million if AstraZeneca accepts ISIS-AZ1$_{Rx}$ as the second development candidate in our collaboration.

During 2012, we earned revenue of $9.3 million from the $25 million upfront payment we received from AstraZeneca in December 2012, which represented nine percent of our total revenue for that period.

Biogen Idec

We have established three strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise. In January 2012, we entered into a global collaboration agreement with Biogen Idec valued at up to $299 million to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million in substantive milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing. We are responsible for developing ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We are eligible to receive up to $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of ISIS-SMN$_{Rx}$. We will earn the next milestone payment of $18 million if we initiate the Phase 2/3 study for ISIS-SMN$_{Rx}$.

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement valued at up to $271 million to develop and commercialize a novel antisense drug targeting, or dystrophia myotonica-protein kinase, or DMPK, for the treatment of DM1. Under the terms of the agreement, we received an upfront payment of $12 million and are eligible to receive up to $59 million in substantive milestone payments associated with the development of the DMPK-targeting drug prior to licensing. We are responsible for global development of the drug through the completion of Phase 2 clinical trials. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. We are also eligible to receive up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for our DMPK program.

In December 2012, we and Biogen Idec entered into a third and separate collaboration valued at more than $630 million to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million and are eligible to receive development milestone payments to support research and development of each program including a $10 million milestone payment per program upon initiation of an IND-enabling toxicology study. We are also eligible to receive up to another $200 million in a license fee and regulatory milestone payments per program including up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

During 2012, we earned revenue of $8.5 million from our relationships with Biogen Idec, which represented eight percent of our total revenue for that period.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. In addition to the $15 million upfront fee, we earned $8 million in milestone payments related to the development of BMS-PCSK9$_{Rx}$. The collaboration ended in December 2011, and we regained the rights to discover and develop antisense drugs to target PCSK9.

During 2012, 2011 and 2010, we earned revenue of $290,000, $2.4 million and $12.2 million, respectively, from Bristol-Myers Squibb, which represented less than one percent, two percent and 11 percent, respectively, of our total revenue for those years.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin, and LY2275796, an antisense inhibitor of eIF-4E. In the second quarter of 2012, Eli Lilly and Company decided not to continue the development of LY2181308. Therefore we will not earn future milestone payments from Eli Lilly and Company associated with LY2181308.

In December 2009, we reacquired LY2275796, which we renamed ISIS-EIF4E$_{Rx}$, and we are continuing to develop the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development. However, if we publicly disclose the results from a Phase 2 clinical study of ISIS-EIF4E$_{Rx}$:

- Eli Lilly and Company may license ISIS-EIF4E$_{Rx}$ on the predefined terms;
- Eli Lilly and Company may tell us it is not interested in licensing ISIS-EIF4E$_{Rx}$, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner; or
- Eli Lilly and Company may offer to license ISIS-EIF4E$_{Rx}$ on terms that are lower than the predefined terms, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company

and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2012, 2011 and 2010, we did not earn any revenue from our relationship with Eli Lilly and Company.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of KYNAMRO. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to KYNAMRO, including the key product related patents described in the "Patents and Proprietary Rights" section under "ApoB 100 and KYNAMRO" on page 33 of this report, and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apo-B by binding to the mRNA encoding apo-B, throughout the world.

The transaction included a $175 million licensing fee, a $150 million equity investment in our stock in which we issued Genzyme five million shares of our common stock, and a share of worldwide profits on KYNAMRO and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. In May 2012, we earned a $25 million milestone payment from Genzyme when the FDA accepted the NDA for KYNAMRO and in January 2013 we earned an additional $25 million milestone payment when the NDA was approved. We may also receive over $1.5 billion in substantive milestone payments if Genzyme achieves pre-specified events, including up to $700 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could earn under our agreement with Genzyme is $25 million upon the earlier of an NDA Approval for the use of KYNAMRO to treat patients who have heterozygous FH or annual net revenue equals or exceeds $250 million in a calendar year.

Under this alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. We agreed to supply the drug substance for KYNAMRO for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for KYNAMRO, including the initial commercial launch supply, and Genzyme will be responsible for the long term supply of KYNAMRO drug substance and finished drug product. As part of the agreement, we contributed the first $125 million in funding for the development costs of KYNAMRO. In 2011, we satisfied our development funding obligation. As such, we and Genzyme shared development expenses equally in 2012. Our shared funding of development expenses will end when KYNAMRO is profitable.

The license and co-development agreement for KYNAMRO will continue in perpetuity unless we or Genzyme terminate it earlier under the following situations:

- Genzyme may terminate the license and co-development agreement at any time by providing written notice to Isis;
- We may terminate the license and co-development agreement on a country-by-country basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize KYNAMRO in the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and Canada; and
- Either we or Genzyme may terminate the license and co-development agreement upon the other party's uncured failure to perform a material obligation under the agreement.

Upon termination of the license and co-development agreement, the license we granted to Genzyme for KYNAMRO will terminate and Genzyme will stop selling the product. In addition, if Genzyme voluntarily terminates the agreement or we terminate the agreement in a country or countries for Genzyme's failure to develop and commercialize KYNAMRO, then the rights to KYNAMRO will revert back to us and we may develop and commercialize KYNAMRO in the countries that are the subject of the termination, subject to a royalty payable to Genzyme.

If we are the subject of an acquisition, then within 180 days following the acquisition, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO license and co-development agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm.

Genzyme has agreed to monthly limits on the number of shares it can sell of the Company's stock that it purchased in February 2008. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the KYNAMRO license and co-development agreement or the date Genzyme holds less than two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During 2012, 2011 and 2010, we earned revenue of $67.6 million, $72.3 million and $66.9 million, respectively, from our relationship with Genzyme, which represented 66 percent, 73 percent and 62 percent, respectively, of our total revenue for those years.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, which covers up to six programs, in which we use our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate rapid development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development.

Under the terms of the original agreement, which includes five programs in addition to the transthyretin, or TTR, program, we are eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR$_{Rx}$. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, and we received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$. We have already received $17.5 million in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$, including the $7.5 million milestone payment we received in February 2013. We are also eligible to earn an additional $50 million in pre-licensing milestone payments associated with

the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, GSK has increased the regulatory and commercial milestone payments we can earn should ISIS-TTR$_{Rx}$ achieve registration and meet certain sales thresholds.

Under the terms of the amended agreement, if GSK successfully develops all six programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $231.5 million for the achievement of development milestones, up to $594.5 million for the achievement of regulatory milestones and up to $545 million for the achievement of commercialization milestones. We will earn the next milestone payment of $2 million upon dosing the 10th patient in the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During 2012, 2011 and 2010, we earned revenue of $8.2 million, $17.7 million and $10.3 million, respectively, from our relationship with GSK, which represented eight percent, 18 percent and nine percent, respectively, of our total revenue for those years.

Satellite Company Collaborations

Through our satellite company collaborations, we expand the reach and potential of RNA-targeting therapeutics into disease areas that are outside of our core focus and advance certain RNA-targeting therapeutic technologies. We refer to these companies as our satellite companies, and this strategy as our satellite company strategy. These relationships provide us with partners who are focused in a particular disease area and who share the common goal of advancing our drugs. In these partnerships, we typically own equity in the company, often as part of the licensing agreement and we also retain the potential to earn milestone payments and royalties.

In addition to our satellite company partners that are advancing RNA-targeting therapeutics, we have satellite company partners who take advantage of our dominant intellectual property estate and leverage our own investments in our core technologies to advance RNA-targeting technologies. These partnerships typically involve a cross-license between us and our partner and allow us to participate in newly emerging approaches to RNA-targeting technologies and augment our active programs in these areas. For example, we co-founded Regulus, a company focused on developing microRNA-targeted therapeutics. Regulus is focused on developing microRNA-targeted therapeutics in cancer, fibrosis, metabolic disorders and inflammatory disorders. Regulus has successfully developed strategic alliances with high-quality partners like Sanofi, GSK, Biogen Idec and AstraZeneca, where we have the potential to receive a portion of future milestone payments and royalty payments.

The value of this strategy is also evident in the broad pipeline of drugs we and our partners are developing to treat a large range of diseases. Using their resources and their expertise, our partners are instrumental in driving the development of antisense drugs that we discovered or co-discovered but fall outside our main areas of focus. We believe that our satellite company strategy allows us to realize opportunities outside of our therapeutic focus while our committed and knowledgeable drug development partner incurs the cost of development and assumes the risk.

Achaogen, Inc.

In 2006, we exclusively outlicensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides Achaogen developed. Aminoglycosides are a class of small molecule antibiotics that inhibit bacterial protein synthesis and that physicians use to treat serious bacterial infections. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli. The compound has also demonstrated activity against MRSA.

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have received $3 million from Achaogen, $500,000 which was in Achaogen securities, as Achaogen has advanced plazomicin in development. In addition, assuming Achaogen successfully develops and commercializes the first two drugs under our agreement, we may receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We are eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin. During 2012 and 2011, we did not earn any revenue from our relationship with Achaogen. During 2010, we earned $2 million in revenue from our relationship with Achaogen, which does not include any revenue from the equity we received from Achaogen. At December 31, 2012 and 2011, we owned less than 10 percent of Achaogen's equity.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. We will earn the next milestone payment of $750,000 if Alnylam initiates a Phase 3 study for TTR. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize ssRNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay if we achieve specified development and regulatory events. As of December 31, 2012, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-targeting drug discovery.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of ssRNAi technology. Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million plus $2.6 million of research and development funding in 2009 and 2010. In November 2010, Alnylam terminated the ssRNAi research program and we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. As a result, any licenses to ssRNAi products we granted to Alnylam under the agreement, and any of Alnylam's obligations to pay milestone payments, royalties or sublicense payments to us for ssRNAi products under the agreement, terminated. We continue to advance the development of ssRNAi technology and during the course of the collaboration, we made improvements in the activity of ssRNAi compounds, including increased efficacy and potency and enhanced distribution.

In 2012, we earned $2.7 million in sublicense revenue when Alnylam licensed our technology to Monsanto Company and Genzyme. In addition, we have the potential to receive a portion of future milestone payments and royalty payments from these licenses. As of December 31, 2012, we have earned a total of $48.1 million from Alnylam resulting from licenses of our technology for the development of RNAi therapeutics and technology that we granted to Alnylam and Alnylam has granted to its partners. During 2012, 2011 and 2010, we earned revenue from our relationship with Alnylam totaling $2.7 million, $375,000 and $10.3 million, respectively, which represented three percent, less than one percent and nine percent, respectively, of our total revenue for those years.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL1102 to Teva Pharmaceutical Industries Ltd. From early 2008 until early 2010, when Teva terminated the licensing agreement for ATL1102, we earned $3.4 million as Teva advanced the development of ATL1102. In March 2010, Teva terminated the licensing agreement for ATL1102 and returned rights to the drug to ATL.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. Over the last three years, ATL has raised approximately $8 million that it is using to advance ATL1103. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009, we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

At December 31, 2012 and 2011, we owned less than 10 percent of ATL's equity. During 2012, we did not earn any revenue from our relationship with ATL. During 2011 and 2010, we earned revenue of $210,000, and $35,000, respectively, from our relationship with ATL.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of UC and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In September 2010, we participated in Atlantic Pharmaceuticals' financing by agreeing to sell to Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. At December 31, 2012 and 2011, we owned approximately 11 percent of Atlantic Pharmaceuticals' equity. Because realization of the upfront equity payment is uncertain, we recorded a full valuation allowance.

Under the agreement, we could receive substantive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $600,000 if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international Named Patient Supply regulations for patients with IBD for which we are receiving royalties. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen. During 2012, we earned $3,000 from our relationship with Atlantic Pharmaceuticals and during 2011 and 2010 we did not earn any revenue from our relationship with Atlantic Pharmaceuticals.

Excaliard Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.

In November 2007, we entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring. We granted Excaliard an exclusive worldwide license for the development and commercialization of certain antisense drugs. Excaliard made an upfront payment to us in the form of equity and paid us $1 million in cash for the licensing of an antisense oligonucleotide drug targeting expression of CTGF that is activated during skin scarring following the wound healing process.

In December 2011, Pfizer Inc. acquired Excaliard. To date, we have received $5.7 million and we are eligible to receive up to an additional $8.4 million in contingent payments upon achievement of various milestones associated with the clinical and commercial progress of EXC 001. In addition, we continue to be eligible for milestone and royalty payments under our licensing agreement for EXC 001. Assuming Pfizer Inc. successfully develops and commercializes EXC 001, we may receive substantive milestone payments totaling up to $47.7 million for the achievement of key development and regulatory milestones, including up to $7.7 million for the achievement of development milestones and up to $40 million for the achievement of regulatory milestones. We will earn the next milestone payment of $1.5 million upon initiation of a Phase 3 study for EXC 001. We are eligible to receive royalties on any product sales of EXC 001.

At December 31, 2012, we owned no equity in Excaliard. During 2012 and 2011, we received $1.3 million and $4.4 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard, which we recorded as a gain on investments. We did not earn any revenue during 2012 and 2011 and during 2010 we earned revenue of $3,000 from our relationship with Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007. iCo is developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy and is currently evaluating it in a Phase 2 study in patients with diabetic retinopathy. We received a $500,000 upfront fee from iCo and may receive substantive milestone

payments totaling up to $48.4 million for the achievement of development and regulatory milestones for multiple indications, including up to $7.9 million for the achievement of development milestones and up to $40.5 million for the achievement of regulatory milestones. We will receive the next milestone payment of $4 million if iCo initiates a Phase 3 study for iCo-007. In addition, we are eligible to receive royalties on any product sales of iCo-007. Under the terms of the agreement, iCo is solely responsible for the development and commercialization of the drug. Over the course of our relationship, iCo has paid us in a combination of cash, common stock and convertible notes. As a result, our ownership in iCo at December 31, 2012 and 2011 was approximately nine percent and 12 percent, respectively. During 2012 we did not earn any revenue from our relationship with iCo and during 2011 and 2010 we earned $7,000 in each period from our relationship with iCo.

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc.

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize custirsen, formerly OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of custirsen. In exchange, OncoGenex agreed to pay us royalties on sales of custirsen and to share consideration it receives from licensing custirsen to a third party, except for consideration OncoGenex receives for the fair market value of equity and reimbursement of research and development expenses.

Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using custirsen and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with custirsen. The key product-related patent that we assigned to OncoGenex was U.S. Patent number 6,900,187 having an expiration date of at least 2020; and the key core antisense technology patents we licensed OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026 and its foreign equivalents pending in Australia, Canada, the European Patent Convention and Japan. In addition, we agreed that so long as OncoGenex or its commercialization partner is using commercially reasonable efforts to develop and commercialize custirsen, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing custirsen or until we terminate the agreement for OncoGenex's uncured failure to make a payment required under the agreement.

In December 2009, OncoGenex granted Teva the exclusive worldwide right and license to develop and commercialize any products containing custirsen and related compounds, with OncoGenex having an option to co-promote custirsen in the United States and Canada, for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in payments OncoGenex may receive from Teva in addition to royalties on any product sales of custirsen ranging between 3.88 percent and seven percent. Under the agreement, this royalty is due on a country- by-country basis until the later of ten years following the first commercial sale of custirsen in the relevant country, and the expiration of the last patent we assigned or licensed to OncoGenex that covers the making, using or selling of custirsen in such country.

To facilitate the execution and performance of OncoGenex's agreement with Teva, we and OncoGenex amended our license agreement primarily to give Teva the ability to cure any future potential breach by OncoGenex under our agreement. As part of this amendment, OncoGenex agreed that if OncoGenex is the subject of a change of control with a third party, where the surviving entity immediately following such change of control has the right to develop and sell custirsen, then a payment of $20 million will be due and payable to us 21 days following the first commercial sale of the product in the United States. Any non-royalty payments OncoGenex previously paid to us are creditable towards the $20 million payment, so as a result of the $10 million payment we received from OncoGenex related to its license to Teva, the remaining amount owing in the event of a change of control as discussed above is a maximum of $10 million.

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us substantive milestone payments totaling up to $3.5 million for the achievement of development and regulatory milestones, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225. As of December 31, 2012, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $500,000 if OncoGenex initiates a Phase 2 study for OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex will pay us substantive milestone payments totaling up to $5.8 million for the achievement of key development and regulatory milestones, including up to $1.3 million for the achievement of development milestones and up to $4.5 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of the drug. In January 2011, we earned a $750,000 milestone payment related to OncoGenex's Phase 2 trial in men with metastatic prostate cancer. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for OGX-427.

During 2011, we earned $750,000 in revenue from our relationship with OncoGenex. During 2012 and 2010, we did not earn any revenue from our relationship with OncoGenex.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-targeting therapeutics. In addition, Regulus has assembled a strong leadership team with corporate management, business and scientific expertise, a board of directors that includes industry leaders in drug discovery and development, and a scientific advisory board that consists of world-class scientists including some of the foremost authorities in the field of microRNA research. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner.

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new biomarker tool for characterizing diseases. Regulus focuses its drug discovery and development efforts in numerous therapeutic areas, including cancer, fibrosis, metabolic disorders and inflammatory disorders.

We and Alnylam co-founded Regulus and we each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, and certain early fundamental patents in the microRNA field. Under this agreement, we are eligible to receive fees and/or royalty payments on microRNA therapeutic products that Regulus or its partners develop. In October 2012 Regulus completed an IPO, in which we participated by purchasing $3 million of Regulus' common stock at the offering price. We remain a significant shareholder with approximately seven million shares, or 17 percent, of Regulus common stock on a fully diluted basis. In the fourth quarter of 2012, we stopped using the equity method of accounting for our investment in Regulus and instead we began accounting for our investment at fair value. In the fourth quarter of 2012, we recorded an $18.4 million gain to reflect the change in our ownership percentage as a result of Regulus' IPO.

Regulus exclusively controls many of the early fundamental patent portfolios in the microRNA-targeting therapeutics field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Our "Crooke" patent estate provides Regulus exclusive rights to product compositions and methods of treatment in the field of microRNA-targeting therapeutics. The Regulus patent estate also includes claims to specific microRNA compositions that are optimized for therapeutic use, as well as therapeutic uses of these microRNA compositions, and exclusive rights to Isis' and Alnylam's chemical modification intellectual property estates for microRNA applications. In total, Regulus' intellectual property portfolio includes over 1,000 patents and patent applications pertaining to microRNA drug products, therapeutic modulation of microRNA, and chemical modifications of oligonucleotides for microRNA therapeutics.

Regulus has successfully developed strategic partnerships with high-quality partners like Sanofi, GSK, Biogen Idec and AstraZeneca. We benefit from Regulus' strategic partnerships because we have the potential to receive a portion of future milestone payments and royalty payments. For example, under Regulus' strategic partnership with Sanofi, we and Alnylam each received 7.5 percent, or $1.9 million, of the $25 million upfront payment and are eligible to receive 7.5 percent of all future milestone payments, in addition to royalties on any product sales. During 2012 and 2011, we did not earn any revenue from our relationship with Regulus. In 2010, we earned $1.9 million from our relationship with Regulus.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and physicians associate a wide variety of conditions including infection, cancer and chronic inflammation with AI. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In May 2012, Xenon selected XEN701, a drug targeting the hepcidin-hemojuvelin pathway, as a development candidate. Xenon may take an exclusive license for the development and worldwide commercialization of XEN701. Under our collaboration agreement with Xenon we may receive up to $296 million in substantive milestone payments upon the achievement of pre-specified milestone events that are met by two independent products, including up to $26 million for the achievement of development milestones, up to $150 million for the achievement of regulatory milestones and up to $120 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of XEN701 and a portion of sublicense revenue. We will earn the next milestone payment of $3 million if Xenon initiates a Phase 2 clinical trial for XEN701.

In August 2012, we and Xenon entered into a separate collaboration to discover and develop an antisense drug targeting sodium channel, voltage-gated, type IX, alpha subunit, or SCN9A. Under our collaboration, we obtained exclusive and non-exclusive licenses to certain Xenon patent rights related to SCN9A. Xenon has the option to license a drug targeting SCN9A through identification of a development candidate. If Xenon exercises its option, Xenon will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. In addition to a license fee, we may receive up to $177 million in substantive milestone payments upon the achievement of pre-specified events, including up to $22 million for the achievement of development milestones, up to $85 million for the achievement of regulatory milestones and up to $70 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of SCN9A and a portion of sublicense revenue. We will earn the next milestone payment of $5 million when Xenon completes studies that are sufficient to support filing an IND for an antisense drug targeting the SCN9A gene.

During 2012 and 2011, we earned revenue of $84,000 and $80,000, respectively, from our relationship with Xenon. During 2010 we did not earn any revenue from our relationship with Xenon.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense drugs through, for example, direct delivery to the CNS. These programs represent opportunities for us and our technology. In some cases, we fund these studies through support from our partners or disease advocacy groups and foundations. For example, we receive external funding support for our ALS and Huntington's disease programs.

CHDI Foundation, Inc.

In August 2011, we renewed our collaboration with CHDI, which we initially entered into in November 2007, to provide us with funding for the discovery and development of an antisense drug for the treatment of Huntington's disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's disease. Under the terms of the new collaboration, we will receive funding from CHDI to identify and conduct IND-enabling studies on an antisense drug targeting the huntingtin gene. If we grant a license to a third party to commercialize our Huntington's disease program, we and CHDI will evenly split the proceeds from the license until CHDI has recouped its funding together with a return determined at a predefined interest rate. Thereafter, we will keep the full amount of any additional proceeds. In addition, CHDI reimbursed us for approximately $1.6 million of research-related expenses we incurred after the earlier collaboration ended in 2010, which we are amortizing over the period of our performance obligation. During 2012, and 2011, we earned revenue of $2.0 million and $2.4 million, respectively, from our relationship with CHDI. In 2010, we did not earn any revenue from our relationship with CHDI.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs in the areas of ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

Technology and Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We believe our patent estate represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our pharmaceutical and satellite company partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc. To date, we have generated more than $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Out-Licensing Arrangements; Royalty Sharing Agreements; Sales of IP

Abbott Molecular Inc.

In January 2009, we sold our former subsidiary, Ibis Biosciences, to Abbott Molecular Inc., or AMI, pursuant to a stock purchase agreement for a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2012, 2011 and 2010 we did not earn any revenue from our relationship with AMI.

Eyetech Pharmaceuticals, Inc. (acquired by Valeant Pharmaceuticals International, Inc.)

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases. Eyetech markets Macugen in the United States and Pfizer Inc. markets the drug outside of the United States. In February 2012, Eyetech was acquired by Valeant Pharmaceuticals International, Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us for the achievement of pre-specified events and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in payments, and our license with Eyetech may also generate additional payments aggregating up to $2.8 million for the achievement of specified regulatory events with respect to the use of Macugen for each additional therapeutic indication. In 2012, 2011 and 2010, we earned $499,000, $790,000 and $567,000, respectively, of revenue related to royalties for Macugen under our license to Eyetech.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. In April 2011, we expanded our relationship with Roche Molecular Systems by granting Roche Molecular Systems a non-exclusive license to additional technology for research and diagnostic uses. During 2012, 2011 and 2010, we earned revenue of $1.0 million, $828,000 and $1.8 million, respectively, from our relationship with Roche Molecular Systems.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense its technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of RNase H patents. During 2012, 2011 and 2010 we earned revenue of $10,000, $10,000 and $20,000, respectively, from our relationship with Idera.

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to ISIS-SMN_{Rx}. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay milestone payments to the University of Massachusetts totaling up to $500,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive from sublicensing its technology, and a royalty on sales of ISIS-SMN_{Rx} in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to ISIS-$FGFR4_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive

license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of ISIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $800,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive from sublicensing the Cold Spring Harbor Laboratory's technology, and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide drugs, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide drugs. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the drugs. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. We are providing the drug substance that is necessary for the initial launch of KYNAMRO and Genzyme will be responsible for the long-term supply of KYNAMRO drug substance. We rely on Genzyme to manufacture the finished drug product for KYNAMRO. Genzyme is offering KYNAMRO in the United States in pre-filled syringes. Genzyme has prepared the initial launch quantities of these pre-filled syringes, and plans to produce future supplies of pre-filled syringes, using one of its own manufacturing facilities.

Due to the growing numbers of our antisense drug development partners and the clinical successes of our antisense drugs, including KYNAMRO, in 2009 we increased our manufacturing capacity by upgrading and optimizing the efficiency of our manufacturing facility. We received European GMP certification of our manufacturing facility in 2012 for production of drug substance to support KYNAMRO commercial launch and our facility is subject to periodic inspection by the FDA to ensure that it is operating in compliance with current GMP, or cGMP, requirements.

Our drug substance manufacturing facility is located in an approximately 28,704 square foot building in Carlsbad, California. We lease this building under a lease that has an initial term ending on December 31, 2031 with an option to extend the lease for up to four additional five-year periods. In addition, we have an approximately 25,792 square foot building that houses support functions for our manufacturing activities. We lease this facility under a lease that has an initial term ending in June 2021 with an option to extend the lease for up to two additional five-year periods.

As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Genzyme, iCo, OncoGenex, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Teva. We believe we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs, as well as meet our current internal research and clinical needs. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we can manufacture antisense drugs at commercially competitive prices.

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the United States and other countries. As of February 11, 2013, we owned or exclusively licensed approximately 1,500 issued patents worldwide.

We own or control patents that provide exclusivity for products in our pipeline and patents that provide exclusivity for our core technology in the field of antisense more generally. Our core technology patents include claims to chemically-modified nucleosides and oligonucleotides as well as antisense drug designs utilizing these chemically-modified nucleosides. These core claims are each independent of specific therapeutic target, nucleic acid sequence, or clinical indication. We also own a large number of patents claiming specific antisense compounds having nucleic acid sequences complementary to therapeutic target nucleic acids, independent of the particular chemical modifications incorporated into the antisense compound. Most importantly, we seek and obtain issued patent claims for each of our drugs. For example, for each of our drugs, we file and seek to obtain claims covering each drug's nucleic acid sequence and precise drug design. In sum, we maintain our competitive advantage in the field of antisense technology by protecting our core platform technology, which applies to most of our drugs, and by creating multiple layers of patent protection for each of our specific drugs in development.

Type of Patent Claim	**Breadth**	**Description**
Chemically Modified Nucleosides and Oligonucleotides	Broadly Applicable	Target and sequence independent
Antisense Drug Design Motifs		Target and sequence independent
Therapeutic Methods		Sequence independent
Antisense Sequence		Chemistry independent
Drug Composition	Specific	Specific claim to drug candidates

Chemically Modified Nucleosides and Oligonucleotides

The most broadly-applicable of our patents are those that claim modified nucleosides and oligonucleotides comprising the modified nucleosides that we incorporate into our antisense drugs to increase their therapeutic efficacy. Nucleosides and chemically-modified nucleosides are the basic building blocks of our antisense drugs, therefore claims that cover any oligonucleotide incorporating one of our proprietary modified nucleosides can apply to a wide array of antisense mechanisms of action as well as several therapeutic targets. Of particular note are our patents covering our proprietary 2'-O-(2-methoxy) ethyl modified nucleosides, incorporated into nearly all of our development compounds, as well as our lead candidate modification for our generation 2.5 compounds, the constrained-ethyl nucleosides, or cEt, nucleosides. In June 2011, Santaris opposed our granted patent in Europe drawn to cEt containing nucleotides and oligonucleotides and we intend to vigorously defend our patent in these proceedings. The following are some of our patents in this category:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	5,914,396	2'-O-MODIFIED NUCLEOSIDES AND PHOSPHORAMIDITES	2016	Covers MOE nucleosides and oligonucleotides containing said nucleotides.
US	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'O-MODIFIED PURINES	2023	Covers certain MOE nucleosides and oligonucleotides containing said nucleotides.
US	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
US	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
US	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
US	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers methods of synthesizing our cEt nucleosides.
EP	EP1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
US	7,547,684	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
US	7,666,854	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.

Antisense Drug Design Motifs

MOE Gapmers

Other Isis patents claim oligonucleotides comprising specific antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular antisense mechanism of action, such as RNase H, RNAi, or splicing. We have designed oligonucleotides incorporating motifs, which we refer to as chimeric compounds or gapmers to exploit the RNase H mechanism to achieve target RNA reduction. Almost all of our drugs, including KYNAMRO, contain this gapmer antisense drug design motif. In fact, we own a U.S. patent that covers each of our second generation antisense drugs until March of 2023. We also have issued patents covering other gapmer drug designs, including our generation 2.2 drug designs which optimize gap size and overall length of the oligonucleotide and methods of lowering a target RNA in an animal with these gapmer compositions. The following patents are some examples of our patents in this category:

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
US	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	Covers 2'-O-alkyl-O-alkyl gapmer oligonucleotides.
US	7,919,472	ENHANCED ANTISENSE OLIGONUCLEOTIDES	2026	Covers methods of lowering a target RNA in an animal with a MOE gapmer with a DNA gap of 12 to 18 nucleotides.
EP	EP2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders

Bicyclic Nucleoside Gapmer Oligonucleotides

In addition, we have pursued claims to antisense drug design motifs incorporating bicyclic nucleoside analogs, which include locked nucleic acids, or LNAs. In June 2011, the European Patent Office, or EPO, granted our claims drawn to short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders. Santaris has opposed this granted patent and we intend to vigorously defend our patent in these proceedings. We have also successfully obtained issued patent claims covering gapmer antisense drug design motifs that incorporate our cEt modified nucleosides. The following patents are some examples of our issued patents and allowed patent applications in this category:

Jurisdiction	Patent/ Application	Title	Expiration	Description of Claims

	No.			
EP	EP2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders
US	7,750,131	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers cEt containing gapmer compounds

Therapeutic Methods of Treatment and Antisense Drug Sequences

In addition to our broad core patents, we also own more than 600 patents, worldwide, with claims to antisense sequences and compounds directed to particular therapeutically important targets or methods of achieving clinical endpoints using these antisense compounds. Target patents may also include claims reciting the specific nucleic acid sequences utilized by our products, independent of chemical modifications and motifs. In addition, our product specific patents typically include claims combining specific nucleic acid sequences with nucleoside modifications and motifs. In this way, we seek patent claims narrowly tailored to protect our products specifically, in addition to the broader core antisense patents described above.

ApoB 100 and KYNAMRO

In 2008, we obtained patent claims in the United States drawn to the use of both single-stranded and double-stranded antisense drugs complementary to any site of the mRNA of human apoB, regardless of chemistry or antisense mechanism of action. The patent provides broad protection of the Isis-Genzyme apoB franchise, including KYNAMRO and potential future follow-on compounds. Similar claims granted in Australia and Japan in 2009 and 2010, respectively. We and Genzyme obtained issued claims to the specific antisense sequence and chemical composition of KYNAMRO in the United States, Australia, South Africa and India and an intent to grant in the European Union. The issued U.S. claims should protect KYNAMRO from generic competition in the United States until at least 2025. We are also pursuing additional patent applications designed to protect KYNAMRO in these and other jurisdictions including Canada and Japan. The table below lists the key issued patent claims designed to protect KYNAMRO in the applicable jurisdiction:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	7,407,943	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Methods of inhibiting expression of apoB, decreasing serum cholesterol, decreasing lipoprotein levels, decreasing serum triglycerides in a human with an antisense compound 12 to 30 nucleotide in length and 100% complementary to human apoB wherein the compound is not a ribozyme.
Australia	2002-326481	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	An isolated oligonucleotide compound 12 to 30 nucleobases in length 100% complementary to at least a 12-nucleobase portion of a nucleic acid molecule having nucleotides 151-12820 of SEQ ID 3 (apoB) which is not a ribozyme and use of such compound in therapy
Japan	4471650	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Use of an antisense oligonucleotide 12 to 30 nucleobases in length and 100% complementary to human apoB having one or more modifications and inhibiting expression of apoB by at least 90% in primary hepatocytes when present at a concentration of 300 nM for preparation of a medicament for decreasing serum cholesterol, and decreasing lipoprotein levels in a human
US	7,511,131	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2025	Antisense sequence and composition of matter of KYNAMRO
EP	EP1569695	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO (Intent to grant)
EP	EP2336318	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO (Intent to grant)
India	219847	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
Australia	2003294281	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
South Africa	2005/03690	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO

Custirsen

Issued claims have been obtained from an application jointly filed by Isis and OncoGenex to protect the specific chemical composition of custirsen in the United States. The issued U.S. claims should protect custirsen from generic competition in the United States until at least 2021. The table below lists the U.S. issued patent:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	6,900,187	TRPM-2 ANTISENSE THERAPY USING AN OLIOGNUCLEOTIDE HAVING 2'-O-(2-METHOXY)ETHYL MODIFICATIONS	2021	Antisense sequence and composition of custirsen

Transthyretin and ISIS-TTR$_{Rx}$

We obtained issued claims covering ISIS-TTR$_{Rx}$ in the United States. The issued U.S. claims should protect ISIS-TTR$_{Rx}$ from generic competition in the United States until at least 2025. We are also pursuing additional patent applications designed to protect ISIS-TTR$_{Rx}$ in the United States and other foreign jurisdictions. The table below lists the current issued U.S. patent protecting ISIS-TTR$_{Rx}$:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	8,101,743	MODULATION OF TRANSTHYRETIN EXPRESSION	2025	Antisense sequence and chemistry of ISIS-TTR$_{Rx}$

In some cases, the patent term can be extended to recapture a portion of the term lost during FDA regulatory review.

RNAi Motifs and Mechanisms - The Crooke Patents

The Crooke Patents, which are the result of the early work by Dr. Crooke and co-workers exploring oligonucleotides that activate double-stranded ribonucleases, or dsRNases, cover chemically-modified, RNA-containing oligonucleotides and methods for exploiting the RNAi pathway with these oligonucleotides until June 2016. We licensed the Crooke Patents to Alnylam for the development of double-stranded therapeutics and to Regulus for the development of microRNA-targeting therapeutics. These patents also provide us with exclusivity in the field of ssRNAi compounds, in which we have made great strides to progress this approach toward a viable therapeutic platform. The following patents have issued out of the Crooke Patent family:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	5,898,031	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Oligonucleotides comprising regions of RNA nucleosides and regions of nucleosides having stabilizing chemical modifications. Such oligonucleotides are suitable for use in single- and double-stranded applications.
US	6,107,094	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Compounds and methods that use oligonucleotides having both RNA nucleosides and chemically modified nucleosides, including methods that rely on a dsRNAse to reduce target RNA and compounds having nucleosides with improved affinity and/or stability.
US	7,432,249	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Pharmaceutical compositions comprising a diluent or carrier and a single-stranded antisense oligonucleotide having a plurality of RNA nucleosides and at least one sugar modification.
US	7,432,250	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Methods for treating a patient by administering an antisense compound having a plurality of RNA nucleosides and at least one sugar modification.
US	7,629,321	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Methods for cleaving a target RNA in a cell by contacting the cell with a single-stranded antisense compound having a plurality of RNA nucleosides and at least one sugar modification.
US	7,695,902	OLIGORIBONUCLEOTIDES FOR CLEAVING RNA	2016	Methods of activating a dsRNase by contacting the dsRNase with a double-stranded antisense oligonucleotide where at least one strand has a plurality of RNA nucleosides and at least one sugar modification. The methods may be performed inside a cell.

Manufacturing Patents

We also own patents claiming methods of manufacturing and purifying oligonucleotides. These patents claim methods for improving oligonucleotide drug manufacturing, including processes for large-scale oligonucleotide synthesis and purification. These methods allow us to manufacture oligonucleotides at lower cost by, for example, eliminating expensive manufacturing steps.

We also rely on trade secrets, proprietary know-how and continuing technological innovation to develop and maintain a competitive position in antisense therapeutics.

Government Regulation

Regulation by government authorities in the United States and other countries is a significant component in the development, manufacture and commercialization of pharmaceutical products and services. In addition to regulations enforced by the FDA and relevant foreign regulatory authorities, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

Extensive regulation by United States and foreign governmental authorities governs our manufacture, development and potential sale of therapeutics. In particular, pharmaceutical products are subject to nonclinical and clinical testing, as well as other approval requirements, by the FDA in the United States under the Federal Food, Drug and Cosmetic Act and other laws and by comparable agencies in those foreign countries in which we conduct business. Various federal, state and foreign statutes also govern or influence the manufacture, safety, labeling, storage, record keeping, marketing and quality of our products. State, local, and other authorities also regulate pharmaceutical manufacturing facilities and procedures.

In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. We received European GMP certification of our manufacturing facility and our facility is subject to periodic inspection by the FDA to ensure that it is operating in compliance with cGMP requirements. Approval of each new drug will require a rigorous manufacturing pre-approval inspection by regulatory authorities.

Competition

Our Business in General

For many of their applications, our drugs will compete with existing therapies for market share. In addition, there are a number of companies pursuing the development of oligonucleotide-based technology and the development of pharmaceuticals utilizing this technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies.

Our products under development address numerous markets. The diseases our drugs target for which we have or may receive regulatory approval will determine our competition. For certain of our products, an important factor in competition may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market are important competitive factors. We expect to compete among products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, reliability, availability, price, reimbursement and patent position.

KYNAMRO

In January 2013, the FDA approved the marketing application for KYNAMRO in the United States for patients with HoFH. Genzyme is also pursuing marketing approval for KYNAMRO in other countries, including Europe. Apheresis and maximally tolerated lipid-lowering therapies, including statins, are the standard of care for homozygous FH patients. Apheresis is a two to four hour process administered two to four times a month that mechanically separates LDL-C from the blood. Because apheresis is an invasive, time-consuming procedure conducted only in specialty centers, it can be difficult for patients to receive this treatment.

We believe that of the drugs that are in development or on the market, KYNAMRO's closest competitor is Juxtapid™. In December 2012, the FDA approved Juxtapid as an oral, once-a-day treatment for patients with HoFH. Juxtapid is a small molecule drug that Aegerion Pharmaceuticals developed and commercialized to limit secretion of cholesterol and triglycerides from the intestines and the liver. The FDA approval for Juxtapid is supported by a Phase 3 study in 29 patients with homozygous FH. Aegerion states that the most common adverse reactions in the Phase 3 study were gastrointestinal, reported by 27 of 29 patients, or 93%. In earlier studies evaluating Juxtapid, patients discontinued use of Juxtapid at a high rate due to gastrointestinal adverse events, such as diarrhea, nausea and vomiting. In addition, some patients experienced elevations in liver enzymes and increased mean levels of fat in the liver, or hepatic fat, both of which Aegerion states it observed in its Phase 3 clinical trial of Juxtapid. Like KYNAMRO, Juxtapid is available only through a REMS program that restricts the access of Juxtapid to only patients with a clinical or laboratory diagnosis consistent with HoFH and both the KYNAMRO and Juxtapid labels contain a Boxed Warning citing the risk of liver toxicity.

In our clinical experience with KYNAMRO, we have seen substantial reductions in LDL-C and reductions in other atherogenic lipids linked to cardiovascular disease. In our Phase 3 studies that evaluated KYNAMRO in more than 250 patients, the most common adverse events patients observed were injection site reactions and flu-like symptoms. We also observed elevations in liver transaminases and moderate median increases in liver fat that appeared to be associated with greater reductions in apoB. We believe that this safety profile supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. KYNAMRO is administered by injection once weekly at home with a prefilled syringe while patients take Juxtapid orally once daily. In addition, to avoid gastrointestinal events, patients on Juxtapid are required to maintain a low fat diet of less than 20% fat and patients are gradually titrated to a maximally tolerated dose. In the Juxtapid label, concurrent use of Juxtapid and common medications for HoFH patients who have cardiovascular disease, including simvastatin and warfarin, need to be closely monitored due to drug-drug interactions with potentially harmful outcomes. KYNAMRO has no restrictions with these medications, which may be advantageous for HoFH patients who are on a broad range of therapies due to the severity of their disease. KYNAMRO sales could be affected if KYNAMRO's product profile is not advantageous when compared to an oral drug, some patients may prefer the oral drug over KYNAMRO. Factors affecting a product's profile may include, efficacy, side effects, pricing and reimbursement.

Aegerion has stated that it is charging up to $293,000 for Juxtapid per patient per year, which is significantly higher than KYNAMRO, which Genzyme is pricing at $3,389 a week or $176,000 a year. Our partner, Genzyme, has extensive experience in bringing medicines to patients with severe and rare diseases. In the United States, Genzyme intends to capitalize on its existing sales and marketing infrastructure within specialized medical communities. In addition, with an existing global commercial infrastructure in the cardiovascular community in Europe we believe that Sanofi and its global presence will aid in the rapid expansion of KYNAMRO into markets throughout the world.

Employees

As of February 11, 2013, we employed 288 people in all of our functions, excluding manufacturing and related departments, which employed 54 people. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of February 11, 2013:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	67	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D.	57	Director, Chief Operating Officer and Secretary
C. Frank Bennett, Ph.D.	56	Senior Vice President, Antisense Research
Richard S. Geary, Ph.D.	55	Senior Vice President, Development
Elizabeth L. Hougen	51	Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D.	51	Senior Vice President, Drug Discovery and Corporate Development

Patrick R. O'Neil, Esq.	39	Senior Vice President, Legal and General Counsel

STANLEY T. CROOKE, M.D., Ph.D.

Chairman, Chief Executive Officer and President

Dr. Crooke is a founder of Isis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of the Board in February 1991. Prior to founding Isis, from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

B. LYNNE PARSHALL, J.D.

Director, Chief Operating Officer and Secretary

Ms. Parshall has served as a Director of Isis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served as our Chief Financial Officer from June 1994 to December 2012. She also serves as our Corporate Secretary and has served in various executive roles since November 1991. Prior to joining Isis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations.

C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

Dr. Bennett was promoted to Senior Vice President, Antisense Research in January 2006. From June 1995 to January 2006, Dr. Bennett served as our Vice President, Research. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions. He is an external member of the Scientific Advisory Board of Experimental Therapeutics Center in Singapore.

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

Dr. Geary was promoted to Senior Vice President, Development in August 2008. From August 2003 to August 2008, Dr. Geary served as our Vice President, Preclinical Development. From November 1995 to August 2003, he held various positions within the Preclinical Development department. Prior to joining Isis in 1995, Dr. Geary was Senior Research Scientist and Group Leader for the bioanalytical and preclinical pharmacokinetics group in the Applied Chemistry Department at Southwest Research Institute.

ELIZABETH L. HOUGEN

Senior Vice President, Finance and Chief Financial Officer

Ms. Hougen was promoted to Senior Vice President, Finance and Chief Financial Officer in January 2013. From January 2007 to December 2012, Ms. Hougen served as our Vice President, Finance and Chief Accounting Officer and from May 2000 to January 2007, she served as our Vice President, Finance. Prior to joining Isis in 2000, Ms. Hougen was Executive Director, Finance and Chief Financial Officer for Molecular Biosystems, Inc., a public biotechnology company.

BRETT P. MONIA, Ph.D.

Senior Vice President, Drug Discovery and Corporate Development

Dr. Monia was promoted to Senior Vice President, Drug Discovery and Corporate Development in January 2012. From February 2009 to January 2012, Dr. Monia served as our Vice President, Drug Discovery and Corporate Development and from October 2000 to February 2009, he served as our Vice President, Preclinical Drug Discovery. From October 1989 to October 2000 he held various positions within our Molecular Pharmacology department.

PATRICK R. O'NEIL, Esq.

Senior Vice President, Legal and General Counsel

Mr. O'Neil was promoted to Senior Vice President, Legal and General Counsel in January 2013. From September 2010 to January 2013, Mr. O'Neil served as our Vice President, Legal and General Counsel and from January 2009 to September 2010, he served as our Vice President, Legal and Senior Transactions Counsel. From October 2001 to January 2009 he held various positions within our Legal department. Prior to joining Isis, Mr. O'Neil was an associate at Cooley LLP.

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually

occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Associated with our Drug Discovery and Development Business

If the market does not accept KYNAMRO or our other drugs, we are not likely to generate revenues or become consistently profitable.

Even though KYNAMRO is approved for HoFH in the United States, and if any of our other drugs is approved for marketing, our success will depend upon the medical community, patients and third party payors accepting our drugs as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities approve KYNAMRO or our other drugs for commercialization, doctors may not use our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for KYNAMRO, and any of our other drugs, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price that we receive for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs unaffordable.

If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.

Our competitors engage in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies engage in developing antisense technology. Our competitors may succeed in developing drugs that are:

- priced lower than our drugs;
- safer than our drugs;
- more effective than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including KYNAMRO, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs, including KYNAMRO.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners to provide this capability.

Regarding KYNAMRO, some competitors are pursuing a development or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion received approval from the FDA to market its MTP inhibitor, Juxtapid, as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and non-high-density-lipoprotein cholesterol in patients with HoFH. Aegerion has also submitted a marketing authorization application for Juxtapid to the European Medicines Agency seeking approval of Juxtapid as an adjunct to a low fat diet and other lipid-lowering therapies to reduce cholesterol in patients with HoFH. Our revenues and financial position will suffer if KYNAMRO cannot compete effectively in the marketplace.

Even if approved, KYNAMRO and any of our other drugs may be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. Even if approved, we may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

- KYNAMRO is approved in the United States as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH;
- the KYNAMRO label contains a Boxed Warning citing a risk of hepatic toxicity; and
- KYNAMRO is available only through a Risk Evaluation and Mitigation Strategy called the KYNAMRO REMS.

In addition, if approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we may lose regulatory approval, or we may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO.

We depend on our collaboration with Genzyme for the development and commercialization of KYNAMRO.

We have entered into a collaborative arrangement with Genzyme to develop and commercialize KYNAMRO.

We entered into this collaboration primarily to:

- fund some of our development activities for KYNAMRO;
- seek and obtain regulatory approvals for KYNAMRO; and
- successfully commercialize KYNAMRO.

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize KYNAMRO, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain additional marketing approvals for and successfully commercialize KYNAMRO. Our collaboration with Genzyme may not continue or result in the successful commercialization of KYNAMRO. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing KYNAMRO, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for KYNAMRO. If Genzyme does not successfully commercialize KYNAMRO, we may receive limited or no revenues for KYNAMRO. In addition, Sanofi's acquisition of Genzyme could disrupt Genzyme or distract it from performing its obligations under our collaboration.

If Genzyme cannot manufacture finished drug product for KYNAMRO or the post-launch supply of the active drug substance for KYNAMRO, KYNAMRO may not achieve or maintain commercial success.

We rely on Genzyme to manufacture the finished drug product for KYNAMRO, including the initial commercial launch supply. In addition, Genzyme is responsible for the long term supply of both KYNAMRO drug substance and finished drug product. Genzyme may not be able to reliably manufacture KYNAMRO drug substance and drug product to support the long term commercialization of KYNAMRO. If Genzyme cannot reliably manufacture KYNAMRO drug substance and drug product, KYNAMRO may not achieve or maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our drugs, including additional approvals for KYNAMRO, we cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including KYNAMRO, before a drug can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. In December 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a negative opinion for Genzyme's marketing authorization application for KYNAMRO for the treatment of patients with HoFH. Genzyme has requested a re-examination of the CHMP opinion. Even though Genzyme has requested a re-examination of the CHMP opinion, and has submitted marketing applications to other regulatory agencies, it is possible that European or other regulatory agencies will not approve KYNAMRO for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including KYNAMRO, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our drugs are not suitable for commercial use we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development

programs. There are ongoing clinical studies for KYNAMRO, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in any additional clinical studies for KYNAMRO and in clinical studies for our other drugs. If any of our drugs in clinical studies, including KYNAMRO, does not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for KYNAMRO and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of KYNAMRO. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Any failure or delay in our clinical studies, including any further studies under our development program for KYNAMRO, could reduce the commercial potential or viability of our drugs.

If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for our drugs, including KYNAMRO, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO.

We depend on third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for the ongoing clinical studies for KYNAMRO. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including any expanded product label for KYNAMRO.

Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2012, we had an accumulated deficit of approximately $907.0 million and stockholders' equity of approximately $182.8 million. Most of the losses resulted from costs incurred in connection with our research and development

programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline, including AstraZeneca, ATL, Atlantic Pharmaceuticals, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer, and Teva Pharmaceutical Industries Ltd. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain regulatory approvals; and
- manufacture, market and sell our drugs.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with Genzyme, GSK, Biogen Idec, and AstraZeneca, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we first anticipated.

For example, a collaborator such as Genzyme, GSK, Biogen Idec or AstraZeneca, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the drug that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for its own drugs.

If any of these occur, it could affect our partner’s commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs, including KYNAMRO.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors’ expectations, including milestones for additional approvals or sales expectations of KYNAMRO, the price of our securities would likely decrease.

For example, in December 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a negative opinion for Genzyme’s marketing authorization application for KYNAMRO for the treatment of patients with HoFH. Genzyme has requested a re-examination of the CHMP opinion.

If we cannot protect our patents or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier or revenue source.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time we have to defend our intellectual property rights. In the event of an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in September 2011 we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. This lawsuit may be costly and may not be resolved in our favor.

If a third party claims that our drugs or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of December 31, 2012, we had cash, cash equivalents and short-term investments equal to $374.4 million. If we do not meet our goals to commercialize KYNAMRO or our other drugs, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- additional marketing approvals and successful commercial launch of KYNAMRO;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we terminated the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or drugs.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2012, the market price of our common stock ranged from $7.02 to $15.61 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to KYNAMRO. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

We depend on Regulus for development of our microRNA technology.

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are ultimately responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus. In addition, Regulus' directors, executive management team, and strategic partners, including Alnylam, Isis, AstraZeneca, GSK, Biogen Idec and Sanofi have agreed that until October 4, 2013, subject to specified exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any shares of Regulus' common stock or securities convertible into or exchangeable or exercisable for any shares of Regulus' common stock.

If a natural or man-made disaster strikes our research, development or manufacturing facilities, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 ²¤₃ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In addition, our collaboration agreement with Genzyme regarding KYNAMRO provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO collaboration agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 12.1 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the economic crisis are uncertain. It is possible that the crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 11, 2013, we occupied three buildings in Carlsbad, California totaling approximately 231,000 square feet of laboratory, manufacturing and office space. Our facilities include a 176,000 square foot facility that we use for our primary research and development activities, a 28,704 square foot manufacturing facility and a 25,792 square foot building adjacent to our manufacturing facility. Our 28,704 square foot facility houses manufacturing suites for our drug development business built to meet cGMP requirements and our 25,792 square foot facility has laboratory and office space that we use to support our manufacturing activities. We lease all three buildings under lease agreements. The leases on our 176,000 square foot facility and our 28,704 square foot manufacturing facility expire in 2031 and have four five-year options to extend. Under these lease agreements, we have the option to purchase the facilities, independent of each other at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. The lease for our 25,792 square foot facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods.

Item 3. Legal Proceedings

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1).

On December 28, 2012, a lawsuit was filed against us and certain of our officers on behalf of a class of purchasers of our common stock. The lawsuit sought unspecified monetary damages and generally included allegations that we and certain of our officers violated laws by conditioning investors to believe KYNAMRO would receive US FDA approval for HoFH through materially false and misleading statements regarding KYNAMRO's safety and efficacy. On February 4, 2013, this case was voluntarily withdrawn without prejudice.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity and Related Stockholder Matters and Issuer Repurchases of Equity Securities

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by The Nasdaq Global Select Market. These prices do not include retail markups, markdowns or commissions.

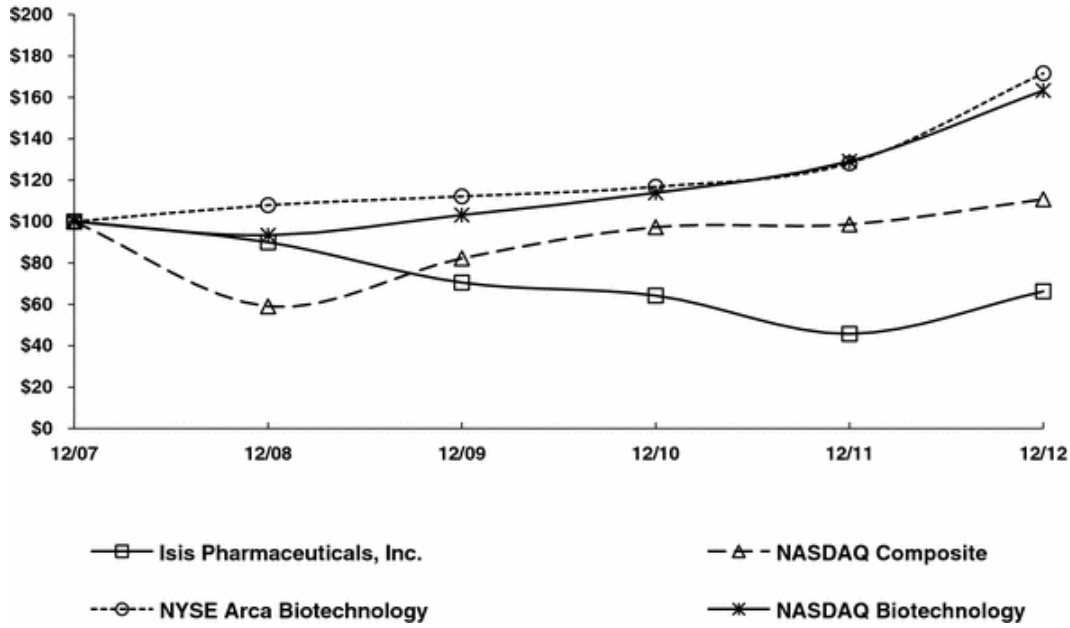
	HIGH	LOW
2012		
First Quarter	$ 9.28	$ 7.08
Second Quarter	$ 12.00	$ 7.02
Third Quarter	$ 15.61	$ 11.45
Fourth Quarter	$ 14.36	$ 7.56
2011		
First Quarter	$ 10.45	$ 8.52
Second Quarter	$ 9.49	$ 8.25
Third Quarter	$ 9.36	$ 6.55
Fourth Quarter	$ 8.67	$ 6.25

As of February 21, 2013, there were approximately 777 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2007 in our common stock, the NASDAQ Composite Index (total return), the NYSE Arca Biotechnology Index and the NASDAQ Biotechnology Index. The total return assumes reinvestment of dividends. In 2012, we elected to include a comparison to the NASDAQ Biotechnology Index. Because the NASDAQ Biotechnology Index is comprised of companies comparable to ours, we believe it provides a more relevant comparison of our stock performance than the NYSE Arca Biotechnology Index. In 2013, we will no longer provide a comparison of our stock performance to the NYSE Arca Biotechnology Index.

Performance Graph (1)

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN
Among Isis Pharmaceuticals, Inc., the NASDAQ Composite Index,
the NYSE Arca Biotechnology Index, and the NASDAQ Biotechnology Index



	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12
Isis Pharmaceuticals, Inc.	$ 100	$ 90	$ 71	$ 64	$ 46	$ 66
NASDAQ Composite Index	$ 100	$ 59	$ 82	$ 97	$ 99	$ 111
NYSE Arca Biotechnology Index	$ 100	$ 108	$ 112	$ 117	$ 128	$ 172
NASDAQ Biotechnology Index	$ 100	$ 93	$ 103	$ 114	$ 129	$ 163

(1) This section is not "soliciting material," is not deemed "filed" with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

Item 6. Selected Consolidated Financial Data (in thousands, except per share amounts):

	Years Ended December 31,				
	2012	2011	2010	2009	2008
Consolidated Statement of Operations Data:					
Revenue(1)	$ 102,049	$ 99,086	$ 108,473	$ 121,600	$ 107,190
Research and development expenses(1)	$ 158,458	$ 157,397	$ 145,160	$ 134,623	$ 106,439
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)	$ (65,478)	$ (84,801)	$ (61,251)	$ (30,562)	$ (9,785)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (65,478)	$ (84,801)	$ (61,251)	$ 155,066	$ (18,172)
Basic and diluted net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)	$ (0.65)	$ (0.85)	$ (0.62)	$ (0.31)	$ (0.10)
Basic and diluted net income (loss) per share attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.65)	$ (0.85)	$ (0.62)	$ 1.58	$ (0.19)
Shares used in computing basic and diluted net income (loss) per share	100,576	99,656	99,143	98,109	94,566

	As of December 31,				
	2012	2011	2010	2009	2008
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments(2)(3)	$ 374,446	$ 343,664	$ 472,353	$ 574,312	$ 490,998
Working capital(2)(3)	$ 349,116	$ 284,027	$ 377,247	$ 484,682	$ 393,685
Investment in Regulus Therapeutics Inc.(3)	$ 33,622	$ —	$ —	$ —	$ —
Total assets(3)	$ 545,686	$ 484,894	$ 550,477	$ 657,184	$ 572,776
Long-term debt and other obligations, less current portion(2)(3)	$ 288,598	$ 232,924	$ 199,175	$ 243,675	$ 300,697
Accumulated deficit(3)	$ (906,966)	$ (841,488)	$ (756,687)	$ (696,150)	$ (851,216)
Noncontrolling interest in Regulus Therapeutics Inc.(3)	$ —	$ —	$ —	$ 10,343	$ 4,737
Noncontrolling interest in Ibis Biosciences, Inc.	$ —	$ —	$ —	$ —	$ 32,419
Investment in Regulus Therapeutics Inc.(3)	$ —	$ 4,424	$ 870	$ —	$ —
Stockholders' equity	$ 182,766	$ 171,434	$ 244,542	$ 302,065	$ 147,380

(1) As a result of the sale of Ibis to AMI in 2009, we have adjusted our revenue; research and development expenses; net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders; and net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders to reflect Ibis' results of operations as discontinued operations in 2009 and 2008.

(2) As a result of the sale of Ibis to AMI, we have adjusted our cash, cash equivalents and short-term investments balance; working capital; and long-term debt and other obligations balance at December 31, 2008 to reflect Ibis' assets and liabilities as assets and liabilities from discontinued operations.

(3) Beginning in the first quarter of 2010, we adopted a new accounting standard and changed our method of accounting for our variable interest in Regulus. We adopted the new standard on a prospective basis; therefore, beginning in the first quarter of 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Under the equity method of accounting, we stopped including Regulus' revenue and operating expenses in our operating results. Instead we included our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our consolidated balance sheet, we presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." In the fourth quarter of 2012, Regulus completed an IPO. We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. In the fourth quarter of 2012, we stopped using the equity method of accounting for our equity investment in Regulus and instead we began accounting for our investment at fair value. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 2, *Investment in Regulus Therapeutics Inc.*

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. Our strategy is to do what we do best—to discover unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer. Our partnering strategy provides us the flexibility to license each of our drugs at the optimal time to maximize the near- and long-term value of each drug. In this way, we can expand our pipeline and our partners' pipelines with antisense drugs that address significant medical needs while remaining small and focused. Our strong financial position is a result of the successful execution of our business strategy as well as our focused research and development capabilities.

Our flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. Marketing applications for KYNAMRO are under review by the EMA and other regulatory authorities. Genzyme is executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare

diseases and plans to leverage its infrastructure in these markets. By concentrating marketing and sales efforts on lipid specialists and physicians who refer patients to these specialists, Genzyme plans to quickly reach patients with HoFH in the United States.

To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec and GSK, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like rare diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. This strategy allows us to develop drugs that could have significant commercial potential with a knowledgeable and committed partner while avoiding the cost of later-stage clinical studies. As in all of our partnerships, we benefit financially from upfront payments, development, regulatory and commercial milestones, licensing fees and royalties from these partnerships. This allows us to expand and broaden our drug discovery efforts to new disease targets in therapeutic areas that are outside of our expertise or in areas where our partners will provide tools and resources that will complement our drug discovery efforts. For example, through our oncology partnership with AstraZeneca, we are capitalizing on AstraZeneca's development experience and research in oncology.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. For example, in 2012, we formed three strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, and a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer. In total during 2012, we received $96 million from Biogen Idec and AstraZeneca in upfront payments and have the potential to earn more than $2 billion in future milestone payments and licensing fees. Since 2007, our partnerships have generated an aggregate of more than $975 million in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our current partnered programs we have the potential to earn $5.1 billion in future milestone payments. We also have the potential to share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, or royalty arrangements.

We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, we benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam and Regulus, a company we co-founded with Alnylam focused on microRNA therapeutics. In October 2012 Regulus completed an initial public offering, in which we participated, bringing our ownership in Regulus to approximately seven million shares of Regulus' common stock, which was valued at approximately $36 million on February 26, 2013. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

We protect our proprietary technologies and products through our substantial patent estate. As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated over $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Business Segments

Prior to 2011, we reported our results in two separate segments: Drug Discovery and Development and Regulus. Beginning in 2011, we stopped considering Regulus as an operating segment because our chief decision making officer stopped reviewing Regulus' operating results for purposes of making resource allocations. Therefore we now only operate in, and will provide financial information and results for, our Drug Discovery and Development operations.

In our Drug Discovery and Development operations we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets we can build a large and diverse portfolio of drugs to treat a variety of health conditions, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer. We have partnered 16 of our 28 drug candidates, which substantially reduces our development costs.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies. For all of these policies, we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the proper valuation of inventory;

- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities; and
- Determining the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In those instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Research and development revenue under collaborative agreements

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services. Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and then accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a standalone basis. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense therapeutics against five cancer targets. As part of the collaboration, we received a $25 million upfront payment and are eligible to receive a $6 million payment in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$. We also granted AstraZeneca options to license up to three drugs under a separate research program. We are responsible for completing an ongoing clinical study of ISIS-STAT3$_{Rx}$ and IND-enabling studies for ISIS-AZ1$_{Rx}$. AstraZeneca will be responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$. In addition, if AstraZeneca exercises its option for any drugs resulting from the research program, AstraZeneca will assume global development, regulatory and commercialization responsibilities for such drug. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that certain deliverables, either individually or in combination, have stand-alone value. Below is a list of the four separate units of accounting under our agreement:

- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-STAT3$_{Rx}$ for the treatment of cancer;
- The development services we will perform for ISIS-STAT3$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AZ1$_{Rx}$ and the research services we will perform for ISIS-AZ1$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we will perform for this program.

We determined that the ISIS-STAT3$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3$_{Rx}$ is currently in development and it is possible that AstraZeneca or another third party could conduct clinical trials without assistance from us. As a result, we consider the ISIS-STAT3$_{Rx}$ license and the development services for ISIS-STAT3$_{Rx}$ to be separate units of accounting. We recognized the revenue allocated to the ISIS-STAT3$_{Rx}$ license on the date of the agreement because that is when we delivered the license. We will recognize the revenue allocated to the development services for ISIS-STAT3$_{Rx}$ over the period of time we perform services. The ISIS-AZ1$_{Rx}$ license is also an exclusive license. Because of the early stage of research for ISIS-AZ1$_{Rx}$, we believe that our knowledge and expertise with antisense technology is essential for AstraZeneca or another third party to successfully develop ISIS-AZ1$_{Rx}$. As a result, we concluded that the ISIS-AZ1$_{Rx}$ license does not have stand-alone value and we combined the ISIS-AZ1$_{Rx}$ license and related research services into one unit of accounting. We will recognize revenue for the combined unit of accounting over the period of time we perform services. We determined that the options under the research program did not have stand-alone value because AstraZeneca cannot develop or commercialize drugs resulting from the research program until AstraZeneca exercises the respective option or options. As a result, we considered the research options and the related research services as a combined unit of accounting. We will recognize revenue for the combined unit of accounting over the period of our performance.

We determined that the allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

We allocated the $25 million upfront payment based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the licenses granted for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for each drug. We then discounted the projected income for each license to present value. The significant inputs we used to determine the projected income of the licenses included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the research and development services by using our internal estimates of the cost to perform the specific services, marked up to include a reasonable profit margin, and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform research and development. The significant inputs we used to determine the selling price of the research and development services included:

- The number of internal hours we will spend performing these services;
- The estimated number and cost of studies we will perform;
- The estimated number and cost of studies that we will contract with third parties to perform; and
- The estimated cost of drug product we will use in the studies.

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment in December 2012 for the ISIS-STAT3$_{Rx}$ license. We are recognizing the remaining $15.7 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $600,000, from the amount we recorded.

Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements. Adjustments to performance periods and related adjustments to revenue amortization periods have had a material impact on our revenue on only one occasion. When Alnylam Pharmaceuticals, Inc. terminated the companies' ssRNAi research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement.

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for developing ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials. In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of Phase 2 clinical trials. In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets. All three of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated the SMA, DMPK, and neurology agreements to determine whether we should account for them as separate agreements or as a single multiple element arrangement. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, the first two agreements cover two different diseases while the targets for the third agreement are yet to be defined, there are no interrelated or interdependent deliverables, there are no provisions in either agreement that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all three of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective research and development term, which is the estimated period of our performance.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans. During the first step of the development stage, we or our partners study our drugs in IND-enabling studies, which are animal studies intended to support an Investigational New Drug, or IND, application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate. The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the FDA and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage. If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing approval such as an NDA in the United States or a MAA in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing approval in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain approval from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with ongoing access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GSK we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In 2012, the FDA accepted the NDA for KYNAMRO. In 2011, we initiated a Phase 1 clinical study on ISIS-TTR$_{Rx}$, the first drug selected as part of our collaboration with GSK and we selected ISIS-AAT$_{Rx}$ as the second development candidate as part of that collaboration. We consider milestones related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Therefore, we recognized the entire $25 million milestone payment from Genzyme for acceptance of the NDA for KYNAMRO in 2012 and the two $5 million milestone payments from GSK in their entirety in 2011. Further information about

our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements* in the Notes to the Consolidated Financial Statements.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Valuation of Investments

We consider all liquid investments with maturities of 90 days or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive loss and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and an investment in equity securities in a publicly-held biotechnology company; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of two publicly-held biotechnology companies for which we calculated a lack of marketability discount because there are restrictions on when we can trade the securities. The majority of our securities have been classified as Level 2. To estimate the fair value of securities classified as Level 2, we utilize the services of a fixed income pricing provider that uses an industry standard valuation model based on a market approach, which considers prices generated by market transactions involving identical or comparable assets. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids. We validate the fair value of securities from our pricing provider by understanding the pricing model they use and comparing their assessment of the fair value of our Level 2 investments to the fair value provided by the custodians of our Level 2 investments. Our pricing provider and custodians use similar techniques to derive fair value for Level 2 securities.

As of December 31, 2012, we classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc. as Level 3. We calculated a lack of marketability discount on the fair value of these securities because there are restrictions on when we can trade the securities.

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. We account for our equity investments in publicly-held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive loss. We account for our equity investments in privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. Most of the cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those circumstances we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

During 2011, we recognized a $4.2 million net gain on investments primarily consisting of the $4.4 million we received for our ownership interest in Excaliard when Pfizer Inc. acquired Excaliard. During 2012 we recognized a $1.5 million net gain on investments primarily consisting of a $1.3 million gain for contingent payments we received from Pfizer Inc. triggered by its decision to advance EXC 001 into a Phase 2 study. See further discussion about our investment in Excaliard in Note 7, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

In addition, in the fourth quarter of 2012, we recorded an $18.4 million gain on our investment in Regulus to reflect the change in our ownership percentage when Regulus completed its IPO. We have reflected this gain in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc." See further discussion about our investment in Regulus in Note 2, *Investment in Regulus Therapeutics Inc.*, in the Notes to the Consolidated Financial Statements.

Valuation of Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and exclusive licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties to determine if any impairment is present. We consider the following factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;

- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and

- Challenges or potential challenges to our existing patents, the likelihood that the United States Patent and Trademark Office, or foreign equivalent, will issue an application and the scope of our issued patents.

We recorded a charge of $817,000, $1.9 million and $1.5 million for the years ended December 31, 2012, 2011 and 2010, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values.

Valuation of Inventory

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs.

Estimated Liability for Clinical Development Costs

We record accrued liabilities related to expenses for which service providers have not yet billed us related to products or services that we have received, specifically related to ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing preclinical and development costs during the period in which we incur such costs, we maintain an accrual to cover these expenses. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

Valuation Allowance for Net Deferred Tax Assets

We record a valuation allowance to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that we will not recognize some or all of the deferred tax assets. Except for 2009, we have had net losses since inception, and as a result, we have established a 100 percent valuation allowance for our net deferred tax asset. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to the valuation allowance.

Convertible Debt

We account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

In August 2012, we completed a $201.3 million offering of convertible senior notes, which mature in 2019 and bear interest at 2¾ percent. We assigned a value to the debt component of our 2¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the debt discount over the life of these 2¾ percent notes as additional non-cash interest expense utilizing the effective interest method. For additional information, see Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

Consolidation of Variable Interest Entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary.

Stock-Based Compensation

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our Employee Stock Purchase Plan, or ESPP, at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period. We estimate forfeitures based on historical experience. There were no material changes to our estimated forfeitures for 2012, 2011 and 2010.

We utilize the Black-Scholes model as our method of valuing stock purchase rights under the ESPP and option awards. We discuss the assumptions we use in our Black-Scholes model in Note 5, *Stockholders' Equity*, in the Notes to the Consolidated Financial Statements. We recognize compensation expense for option awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. We base our risk-free interest rate assumption on

observed interest rates appropriate for the term of our employee stock options and our ESPP. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use an average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns.

In 2012, we began granting RSUs to our employees and our board of directors. The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period.

As of December 31, 2012, total unrecognized compensation cost related to non-vested stock-based compensation plans and RSUs were $5.5 million and $1.3 million, respectively. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost for stock options and RSUs over a weighted average period of 1.1 years and 3.1 years, respectively.

Results of Operations

Years Ended December 31, 2012 and December 31, 2011

Revenue

Total revenue for the year ended December 31, 2012 was $102.0 million compared to $99.1 million for 2011. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, in 2012, we recognized revenue from new sources in connection with the license for ISIS-STAT3$_{Rx}$ which we granted to AstraZeneca under our recently announced strategic alliance on RNA therapeutics for cancer, our three new collaborations with Biogen Idec and the KYNAMRO FDA acceptance milestone from Genzyme. At the same time, in 2012, revenue from amortization of the upfront payments associated with the Genzyme collaboration ended as planned midyear.

We earned a $25 million milestone payment from Genzyme in January 2013 for FDA approval of KYNAMRO and a $7.5 million milestone payment from GSK in February 2013 for the initiation of a Phase 2/3 study for ISIS-TTR$_{Rx}$. We will reflect both of these milestone payments in our first quarter 2013 financial results.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2012 was $99.1 million compared to $96.2 million for 2011. In 2012, we recognized revenue from new sources in connection with our collaboration with AstraZeneca, our three new collaborations with Biogen Idec and the KYNAMRO FDA acceptance milestone from Genzyme. At the same time, in 2012, revenue from amortization of the upfront payments associated with the Genzyme collaboration ended as planned midyear.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was unchanged at $2.9 million for the year ended December 31, 2012 and December 31, 2011.

Operating Expenses

Operating expenses for the year ended December 31, 2012 were $171.0 million compared to $170.2 million for 2011. In 2012, we were able to advance and expand our pipeline while maintaining our operating expenses essentially flat to 2011. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs.

The following table sets forth information on research and development expenses (in thousands):

	Year Ended December 31,	
	2012	2011
Research and development expenses	$ 151,212	$ 148,870
Non-cash compensation expense related to equity awards	7,246	8,527
Total research and development	$ 158,458	$ 157,397

For the year ended December 31, 2012, we incurred total research and development expenses of $151.2 million compared to $148.9 million for 2011. Research and development expenses in 2012 were slightly higher primarily due to higher development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs and contribute to the advancement of the science by funding core antisense technology research.

Our antisense drug discovery expenses were as follows (in thousands):

	Year Ended December 31,	
	2012	2011
Antisense drug discovery expenses	$ 34,035	$ 32,618
Non-cash compensation expense related to equity awards	2,108	2,433
Total antisense drug discovery	$ 36,143	$ 35,051

Antisense drug discovery costs were $34.0 million for the year ended December 31, 2012, and increased slightly compared to $32.6 million for 2011. The higher expenses in 2012 compared to 2011 were primarily due to an increase in personnel expenses and an increase in research services provided by third parties to support our partnered research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2012	2011
KYNAMRO	$ 10,920	$ 13,719
Other antisense development products	54,291	47,395
Development overhead costs	5,350	5,708
Non-cash compensation expense related to equity awards	2,482	2,908
Total antisense drug development	$ 73,043	$ 69,730

Antisense drug development expenditures were $70.6 million for the year ended December 31, 2012 compared to $66.8 million for 2011. The higher expenses in 2012 were primarily due to an increase in development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that

time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. We have partnered 16 of our 28 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. In 2011, we satisfied our $125 million development funding obligation. As such, we and Genzyme shared development costs equally in 2012. Our shared funding of development expenses will end when KYNAMRO is profitable.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Year Ended December 31,	
	2012	2011
Manufacturing and operations	$ 19,232	$ 19,506
Non-cash compensation expense related to equity awards	999	1,101

Total manufacturing and operations	$ 20,231	$ 20,607

Manufacturing and operations expenses for the year ended December 31, 2012 were $19.2 million and decreased slightly compared to $19.5 million for 2011. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support costs.

The following table sets forth information on R&D support costs (in thousands):

	Year Ended December 31,	
	2012	2011
Personnel costs	$ 9,231	$ 8,665
Occupancy	6,909	9,446
Depreciation and amortization	5,171	7,894
Insurance	1,143	884
Other	4,930	3,035
Non-cash compensation expense related to equity awards	1,657	2,085
Total R&D support costs	$ 29,041	$ 32,009

R&D support costs for the year ended December 31, 2012 were $27.4 million compared to $29.9 million for 2011. The decrease in 2012 compared to the same period in 2011 was primarily because the leases on our former research and development facilities expired at the end of 2011 and as a result we recorded less rent expense in 2012. Although our rent expense was lower, we had higher interest expense in 2012 because accounting rules required us to record the cost of our current primary research and development facility as a fixed asset with a corresponding liability, which is discussed below in *Interest Expense*. Other significant decreases in R&D support costs were due to a decrease in depreciation and amortization because of non-cash charges for patents and patent applications that we wrote off in 2011 and a change in the amortization period we made in 2011 for a license agreement offset, in part, by an increase in litigation costs related to our patent infringement lawsuit against Santaris Pharma A/S. All amounts exclude non-cash compensation expense related to equity awards.

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of legal, human resources, investor relations, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

The following table sets forth information on general and administrative expenses (in thousands):

	Year Ended December 31,	
	2012	2011
General and administrative expenses	$ 11,190	$ 11,471
Non-cash compensation expense related to equity awards	1,325	1,318
Total general and administrative	$ 12,515	$ 12,789

General and administrative expenses for the year ended December 31, 2012 were $11.2 million and decreased slightly compared to $11.5 million for 2011. All amounts exclude non-cash compensation expense related to equity awards.

Investment in Regulus Therapeutics Inc.

Our equity in net loss of Regulus for the year ended December 31, 2012 was $1.4 million compared to $3.6 million for 2011. Our equity in net loss of Regulus decreased because in 2012 we suspended recognizing losses in our share of Regulus' net loss. Until the completion of Regulus' IPO in October 2012, we and Alnylam were guarantors of both of the convertible notes that Regulus issued to GSK. Therefore, we continued to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed. In the second quarter of 2012, we suspended recording our portion of Regulus' net loss because our share of Regulus' net loss exceeded the amount we had guaranteed.

In the fourth quarter of 2012, as a result of the IPO, we recorded an $18.4 million gain to reflect the change in our ownership percentage as a result of Regulus' IPO. We have reflected this gain in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc." Also, in the fourth quarter of 2012 we stopped using the equity method of accounting for our equity investment in Regulus and instead we began accounting for our investment at fair value.

Investment Income

Investment income for the year ended December 31, 2012 totaled $1.8 million compared to $2.4 million for 2011. The decrease in investment income was primarily due to lower average cash balance and current market conditions. Our average cash balance was lower in 2012 than in 2011, even though we ended 2012 with more cash than we had at the end of 2011, because of a significant inflow of cash in the fourth quarter of 2012.

Interest Expense

Interest expense for the year ended December 31, 2012 totaled $21.2 million compared to $16.7 million for 2011. The increase in interest expense in 2012 is primarily a result of additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility. The increase is also due to higher interest expense for our convertible notes because in 2012 we used the proceeds from our 2¾ convertible notes to redeem the entire outstanding amount of our 2⅝ percent convertible notes. See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information about our convertible notes and long-term liability for our primary research and development facility.

Gain on Investments, Net

Net gain on investments for the year ended December 31, 2012 was $1.5 million compared to $4.2 million for 2011. The net gain on investments in 2012 consists primarily of a $1.3 million gain we recorded for contingent payments we received from Pfizer Inc. triggered by its decision to advance EXC 001 into a Phase 2 study. The net gain on investments in 2011 consists primarily of the $4.4 million we received for our ownership interest in Excaliard when Pfizer Inc. acquired Excaliard. See further discussion about our investments in Excaliard in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Early Retirement of Debt

In September 2012, we redeemed our 2⅝ percent convertible subordinated notes. The carrying value of the 2⅝ percent notes on our balance sheet included a discount based on the estimated fair value of similar debt instruments without the conversion feature. We were amortizing this discount over the expected life of the debt as additional non-cash interest expense. As a result of our early redemption of the 2⅝ percent notes, we recognized a $4.8 million loss primarily related to a non-cash write-off of the unamortized portion of the debt discount and debt issuance costs. See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information about our redemption of the 2⅝ percent notes.

Income Tax Benefit

In 2012, we recorded a tax benefit of $9.1 million, which reflected our application of the intraperiod tax allocation rules under which we are required to record a tax benefit in continuing operations to offset the tax provision we recorded directly to other comprehensive income primarily related to the unrealized gain on our investment in Regulus because we are now accounting for our investment at fair value.

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2012 was $65.5 million compared to $84.8 million for 2011. Basic and diluted net loss per share for the year ended December 31, 2012 was $0.65 per share compared to $0.85 per share for 2011. Our net loss for 2012 was significantly lower than 2011 primarily due to the $18.4 million gain from our investment in Regulus and the related $9.1 million income tax benefit offset, in part, by an increase in our net operating loss, the $4.8 million loss on the early retirement of our 2¤8 percent convertible subordinated notes, additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility, and slightly higher interest expense related to our convertible notes.

Net Operating Loss Carryforward

At December 31, 2012, we had federal and California tax net operating loss carryforwards of approximately $636.9 million and $561.2 million, respectively. We also had federal and California research credit carryforwards of approximately $44.2 million and $18.4 million, respectively. Our federal and California tax loss carryforwards expire at various dates starting in 2014, unless we utilize them before then. Our net operating loss and tax credit carryforwards may be subject to an annual limitation regarding utilization against taxable income in future periods due to “change of ownership” provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards.

Years Ended December 31, 2011 and December 31, 2010

Revenue

Total revenue for the year ended December 31, 2011 was $99.1 million compared to $108.5 million for 2010. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, revenue in 2011 included $17.7 million in revenue from GSK, compared to $10.3 million in 2010, primarily due to the timing of milestone payments. This increase in revenue was offset by less revenue from Bristol-Myers Squibb and Alnylam compared to 2010 because we were no longer amortizing the upfront fees. Revenue in 2011 also included $5.8 million of commercial revenue for drug substance that we sold to Genzyme to support the commercial launch of KYNAMRO.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2011 was $96.2 million compared to $102.9 million for 2010. Lower revenue in 2011 compared to 2010 was primarily due to the timing of milestone payments and less amortization of upfront fees. Milestones earned from GSK in 2011 included a $5 million milestone in the second quarter of 2011 for the initiation of a Phase 1 study for ISIS-TTR$_{Rx}$ and a $5 million milestone in the fourth quarter of 2011 for designating ISIS-AAT$_{Rx}$ as a development candidate.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2011 was $2.9 million compared to $5.6 million for 2010. The decrease primarily related to $1.9 million of sublicense revenue we earned from Regulus in the second quarter of 2010 related to its strategic alliance with

Sanofi.

Operating Expenses

Operating expenses for the year ended December 31, 2011 were $170.2 million compared to $156.8 million for 2010. Our operating expenses in 2011 reflected moderately higher development costs associated with our maturing pipeline of drugs. These increases were offset by lower non-cash compensation expense related to equity awards resulting from a decrease in the average price of Isis' stock in 2011.

In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs.

The following table sets forth information on research and development costs (in thousands):

	Year Ended December 31,	
	2011	2010
Research and development expenses	$ 148,870	$ 135,012
Non-cash compensation expense related to equity awards	8,527	10,148
Total research and development	$ 157,397	$ 145,160

For the year ended December 31, 2011, we incurred total research and development expenses of $148.9 million compared to $135.0 million for 2010. Research and development expenses in 2011 reflected moderately higher costs associated with our maturing pipeline of drugs offset by lower costs associated with the completion of the KYNAMRO Phase 3 program to support the initial regulatory filings. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

Our antisense drug discovery expenses were as follows (in thousands):

	Year Ended December 31,	
	2011	2010
Antisense drug discovery	$ 32,618	$ 33,175
Non-cash compensation expense related to equity awards	2,433	2,941
Total antisense drug discovery	$ 35,051	$ 36,116

Antisense drug discovery costs were $32.6 million for the year ended December 31, 2011, and decreased slightly compared to $33.2 million for 2010. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2011	2010
KYNAMRO	$ 13,719	$ 25,807
Other antisense development products	47,395	29,907
Development overhead costs	5,708	4,713
Non-cash compensation expense related to equity awards	2,908	3,207
Total antisense drug development	$ 69,730	$ 63,634

Antisense drug development expenditures were $66.8 million for the year ended December 31, 2011 compared to $60.4 million for 2010. The higher expenses in 2011 were primarily due to moderately higher costs associated with our maturing pipeline of drugs as these drugs move forward to more advanced stages of development, including into larger, longer clinical studies. These increases were offset by lower costs associated with the completion of the KYNAMRO Phase 3 program to support the initial regulatory filings. All amounts exclude non-cash compensation expense related to equity awards.

Manufacturing and Operations

Our manufacturing and operations expenses were as follows (in thousands):

	Year Ended December 31,	
	2011	2010
Manufacturing and operations	$ 19,506	$ 17,513
Non-cash compensation expense related to equity awards	1,101	1,425
Total manufacturing and operations	$ 20,607	$ 18,938

Manufacturing and operations expenses for the year ended December 31, 2011 were $19.5 million compared to $17.5 million for 2010. The increase in expenses was a result of increases in the cost of raw materials used to manufacture our generation 2.5 compounds, services provided by third parties and personnel costs to support our expanded clinical development programs including KYNAMRO. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

The following table sets forth information on R&D support costs (in thousands):

	Year Ended December 31,	
	2011	2010
Personnel costs	$ 8,665	$ 8,153
Occupancy	9,446	6,587
Depreciation and amortization	7,894	6,394
Insurance	884	922
Other	3,035	1,840
Non-cash compensation expense related to equity awards	2,085	2,576
Total R&D support costs	$ 32,009	$ 26,472

R&D support costs for the year ended December 31, 2011 were $29.9 million compared to $23.9 million for 2010. The increase in expenses in 2011 compared to 2010 primarily relates to one-time occupancy and relocation costs associated with the move to our primary research and development facility, additional depreciation costs and property taxes we recorded in 2011 for our primary research and development facility, and a reduction in the costs we allocated to Regulus in 2011 compared to 2010. When Regulus moved to a separate facility in the second half of 2010, we significantly reduced the amount we were charging them for facilities and support. All amounts exclude non-cash compensation expense related to equity awards.

General and Administrative Expenses

The following table sets forth information on general and administrative expenses (in thousands):

	Year Ended December 31,	
	2011	2010
General and administrative expenses	$ 11,471	$ 9,658
Non-cash compensation expense related to equity awards	1,318	2,011
Total general and administrative	$ 12,789	$ 11,669

General and administrative expenses for the year ended December 31, 2011 were $11.5 million compared to $9.7 million for 2010. The increase in expenses in 2011 compared to 2010 primarily relates to higher personnel costs, one-time occupancy and relocation costs associated with the move to our primary research and development facility, and a reduction in the amount we charged to Regulus for general and administrative support. All amounts exclude non-cash compensation expense related to equity awards.

Investment in Regulus Therapeutics Inc.

Our equity in net loss of Regulus for the year ended December 31, 2011 was $3.6 million compared to $6.9 million for 2010. The decrease was primarily due to a decrease in Regulus' net loss in 2011 compared to 2010. Regulus' net loss decreased in 2011 compared to 2010 primarily due to higher expenses in 2010 related to Regulus' continued efforts to build its team to support its programs and $3.8 million of expense for sublicense fees paid to us and Alnylam from Regulus' strategic alliance with Sanofi offset, in part, by amortization of the upfront fees Regulus received from Sanofi and GSK in 2010.

In 2010, we recorded a $4.7 million gain to reflect the change in our ownership percentage due to the $10 million investment Sanofi made in Regulus. This gain was reflected in our equity in net loss of Regulus line item on our Consolidated Statements of Operations. In 2012, to conform to current period presentation, we have reflected this gain in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc."

Investment Income

Investment income for the year ended December 31, 2011 totaled $2.4 million compared to $3.4 million for 2010. The decrease in investment income was primarily due to a lower average return on our investments resulting from the current market conditions and a lower average cash balance.

Interest Expense

Interest expense for the year ended December 31, 2011 totaled $16.7 million compared to $13.2 million for 2010. The increase in interest expense in 2011 is a result of additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility.

See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information about the accounting treatment for our primary research and development facility.

Gain (Loss) on Investments, Net

Net gain on investments for the year ended December 31, 2011 was $4.2 million compared to a net loss on investments of $713,000 for 2010. The net gain on investments in 2011 consists primarily of the $4.4 million gain we recorded in the fourth quarter of 2011 from our ownership interest in Excaliard when Pfizer Inc. acquired Excaliard. The net loss on investments in 2010 primarily consisted of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL. See further discussion about our investments in these satellite companies in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2011 was $84.8 million compared to $61.3 million for 2010. Basic and diluted net loss per share for the year ended December 31, 2011 was $0.85 per share compared to $0.62 per share for 2010. Our net loss for 2011 increased compared to 2010 primarily due to an increase in our net operating loss, interest expense, and in our share of Regulus' net loss, all of which we discuss above.

Net Operating Loss Carryforward

At December 31, 2011, we had federal and California tax net operating loss carryforwards of approximately $510.6 million and $428.1 million, respectively. We also had federal and California research credit carryforwards of approximately $42.9 million and $16.0 million, respectively.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2012, we have earned approximately $1.1 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through December 31, 2012, we have raised net proceeds of approximately $833.6 million from the sale of our equity securities and we have borrowed approximately $784.3 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2012, we had cash, cash equivalents and short-term investments of $374.4 million and stockholders' equity of $182.8 million. In comparison, we had cash, cash equivalents and short-term investments of $343.7 million and stockholders' equity of $171.4 million at December 31, 2011. At December 31, 2012, we had consolidated working capital of $349.1 million compared to $284.0 million at December 31, 2011. During 2012, we received a substantial amount of cash, including $96 million in upfront payments from Biogen Idec and AstraZeneca, a $25 million milestone payment from Genzyme for FDA acceptance of the KYNAMRO NDA and approximately $30 million in net proceeds from the issuance of our 2¾ percent convertible notes. The significant increase in working capital is primarily due to the cash we received in 2012 and an increase in current assets resulting from our investment in Regulus because we are now recording our investment at fair value. At December 31, 2012, the carrying value of our investment in Regulus was $33.6 million.

As of December 31, 2012, our debt and other obligations totaled $284.1 million compared to $239.9 million at December 31, 2011. The increase was primarily related to the issuance of our 2¾ percent convertible notes in the third quarter of 2012, the proceeds of which we used to redeem the entire outstanding amount of our 2⁵⁄₈ percent convertible notes. In addition, we made an additional draw down of $9.1 million on our equipment financing arrangement in 2012. These increases were offset, in part, by the rent and principal payments we made in 2012 on our lease obligations and notes payable, see Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

The following table summarizes our contractual obligations as of December 31, 2012. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2¾ percent Convertible Senior Notes (principal and interest payable)	$ 240.0	$ 5.6	$ 11.1	$ 11.1	$ 212.2
Facility Rent Payments	$ 143.7	$ 5.8	$ 12.3	$ 13.1	$ 112.5
Equipment Financing Arrangements (principal and interest payable)	$ 10.6	$ 5.0	$ 5.6	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.4	$ 0.1	$ 0.1	$ 0.1	$ 1.1
Capital Lease	$ 0.6	$ 0.2	$ 0.4	$ —	$ —
Operating Leases	$ 27.5	$ 1.4	$ 2.7	$ 2.8	$ 20.6
Total	$ 423,8	$ 18.1	$ 32.2	$ 27.1	$ 346.4

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have facility leases, equipment financing arrangements and other obligations.

In August 2012, we completed a $201.3 million convertible debt offering, which raised proceeds of approximately $194.7 million, net of $6.6 million in issuance costs. The $201.3 million of convertible senior notes mature in 2019 and bear interest at 2¾ percent, which is payable semi-annually. We used a substantial portion of the net proceeds from the issuance of these notes to redeem the entire $162.5 million in principal of our 2⅝ percent convertible subordinated notes. The 2¾ percent notes are convertible under certain conditions, at the option of the note holders, into approximately 12.1 million shares of our common stock at a conversion price of $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a

combination of both. We can redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion

price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 2¾ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent. As of December 31, 2012, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.57 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at December 31, 2012 and 2011 was $10.0 million and $5.3 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed a new facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. We are depreciating the building over its economic life and we will apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2012 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Item 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a) (1) and (2), and incorporate them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

There have been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2012 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

Based on our evaluation as of the end of the period covered by this report on Form 10-K, our principal executive officer and principal financial officer have concluded that our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) were effective as of December 31, 2012 to ensure that information required to be disclosed in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms.

Management’s Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f). Our internal control over financial reporting is a process designed under the supervision of our chief executive officer and chief financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external purposes in accordance with United States generally accepted accounting principles.

As of December 31, 2012, our management, with the participation of the chief executive officer and chief financial officer, assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting established in "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission. Based on the assessment, our management determined that we maintained effective internal control over financial reporting as of December 31, 2012.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2012, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

The above evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Isis Pharmaceuticals, Inc.

We have audited Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2012, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Isis Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2012, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2012 and 2011, and the related statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2012 of Isis Pharmaceuticals, Inc. and our report dated February 28, 2013 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2013

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "ELECTION OF DIRECTORS," including in particular the information under "Nominating, Governance and Review Committee" and "Audit Committee," contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 26, 2013 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2013 Annual Meeting of Stockholders to be held on June 25, 2013.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics and Business Conduct" contained in the Proxy Statement. We have filed our Code of Ethics as an exhibit to our Report on Form 10-K for the year ended December 31, 2009.

Item 1, Part I of this Report contains information concerning our executive officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, from the information under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption "EXECUTIVE COMPENSATION," "Compensation Committee Interlocks and Insider Participation" and "COMPENSATION COMMITTEE REPORT" contained in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

We incorporate by reference the information required by this item to the information under the captions "SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT" contained in the Proxy Statement.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2012.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	8,895,220	$ 10.51	4,149,432(c)
Equity compensation plans not approved by stockholders(b)	2,116,621	$ 14.34	—
Total	11,011,841	$ 11.25	4,149,432

(a) Consists of four Isis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan and ESPP.

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below. The 2000 Broad-Based Equity Incentive Plan expired on January 5, 2010.

(c) Of these shares, 217,087 remained available for purchase under the ESPP as of December 31, 2012. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non-statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2012, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 2,116,621 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 3,442,568 shares under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the option holder's employment or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our board of directors will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

Item 13. Certain Relationships and Related Transactions, and Director Independence

We incorporate by reference the information required by this item to the information under the captions “Independence of the Board of Directors” and “Certain Relationships and Related Transactions” contained in the Proxy Statement.

Item 14. Principal Accountant Fees and Services

We incorporate by reference the information required by this item to the information under the caption “RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS” contained in the Proxy Statement.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 75.

(b) Exhibits

We listed the exhibits required by this Item under Item 15(a)(3).

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 28th day of February, 2013.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke and Elizabeth L. Hougen, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any

amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 28, 2013
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer and Secretary	February 28, 2013
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 28, 2013
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 28, 2013
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 28, 2013
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 28, 2013
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 28, 2013

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006. (2)
3.3	Amended and Restated Bylaws. (14)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock. (13)
4.2	Specimen Common Stock Certificate. (1)
4.3	Stock Purchase Agreement between the Registrant and Genzyme Corporation dated January 7, 2008. (5)
4.4	Indenture, dated as of August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2 ¾ percent Convertible Senior Note due 2019. (31)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.
10.2*	Registrant's 1989 Stock Option Plan, as amended. (29)
10.3*	Registrant's Amended and Restated Employee Stock Purchase Plan. (16)
10.4	Form of Employee Assignment of Patent Rights. (1)
10.5*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement. (7)
10.6	Drug Development and License Option Agreement dated December 2, 2009 between the Registrant and Eli Lilly and Company. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (26)
10.7	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (6)
10.8	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (15)
10.9	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (9)
10.10	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

(11)

10.11	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (5)
10.12	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (26)

10.13	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (18)
10.14	Lease Agreement between the Registrant and BMR-Gazelle Court LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (27)
10.15	Second Amendment to Lease Agreement dated May 15, 2011 between the Registrant and BMR-Gazelle Court LLC, with First Amendment to Lease Agreement included. (11)
10.16	Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005. (19)
10.17*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. (29)
10.18*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement. (23)
10.19*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. (33)
10.20*	Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. (17)
10.21*	Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and B. Lynne Parshall. (17)
10.22	Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 between the Registrant and Alnylam Pharmaceuticals, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (22)
10.23*	Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (21)
10.24	Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc. (25)
10.25*	Form of Option Agreement for Options granted under the 2011 Equity Incentive Plan. (31)
10.26*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan. (31)
10.27	Second Amendment to Lease Agreement between the Registrant and BMR-2282 Faraday Avenue LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (27)
10.28*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan. (12)
10.29*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan. (12)
10.30*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan. (12)
10.31	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (27)

10.32	First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009. (26)
10.33	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC. (19)
10.34	Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (25)
10.35	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (3)
10.36	Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated January 1, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request

for confidential treatment. (4)

10.37	Amendment No. 1 to Amended and Restated License Agreement between the Registrant and OncoGenex Technologies Inc. dated December 18, 2009. (26)
10.38	Amendment Number One to the Amended and Restated License and Collaboration Agreement dated June 10, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (28)
10.39	Second Amendment to Loan Agreement dated November 15, 2010 between the Registrant and RBS Asset Finance, Inc. (24)
10.40	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)
10.41	Third Amendment to Loan Agreement dated June 24, 2012 between the Registrant and RBS Asset Finance, Inc. (33)
10.42	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)
10.43	Letter Agreement Amendment between the Registrant and Alnylam Pharmaceuticals, Inc. dated August 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)
10.44	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.45	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.46	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
14.1	Registrant's Code of Ethics and Business Conduct. (21)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney. (37)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.

31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement. (11)
101	The following financial statements from the Isis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2012, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of stockholders' equity, (iv) consolidated statements of cash flows, and (v) notes to consolidated financial statements (detail tagged).

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

(2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.

(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011 and incorporated herein by reference.

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2009 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

(9) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2008 and incorporated herein by reference.

(10) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference.

(11) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

(12) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

(13) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 14, 2011 and incorporated herein by reference.

(14) Filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.

(15) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2009 Annual Meeting of Stockholders, filed with the SEC on April 20, 2008, and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 5, 2008 and incorporated herein by reference.

(17) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2008 and incorporated herein by reference.

(18) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2005 and incorporated herein by reference.

(19) Filed as an exhibit to the Registrant's Report on Form 8-K filed January 4, 2002 and incorporated herein by reference.

(20) Filed as an exhibit to the Registrant's Notice of 2011Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 28, 2011, and incorporated herein by reference.

(21) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2009 and incorporated herein by reference.

(22) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

(23) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2010 and incorporated herein by reference.

(24) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2008 and incorporated herein by reference.

(25) Filed as an exhibit to the Registrant's Annual Report as Form 10-K for the year ended December 31, 2009 and incorporated herein by reference.

(26) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference.

(27) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2010 and incorporated herein by reference.

(28) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2012 Annual Meeting of Stockholders, filed with the SEC on April 16, 2012, and incorporated herein by reference.

(29) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2010, reference is made to page 70.

(30) Filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed with the SEC on August 8, 2011, and incorporated herein by reference.

(31) Filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.

(32) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference.

(33) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.

(34) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2012 and incorporated herein by

reference.

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

ISIS PHARMACEUTICALS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Isis Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2012 and 2011, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2012. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc. at December 31, 2012 and 2011, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2012, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2012, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 28, 2013 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2013

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	December 31, 2012	December 31, 2011
ASSETS		
Current assets:		
Cash and cash equivalents	$ 124,482	$ 65,477
Short-term investments	249,964	278,187
Contracts receivable	522	6,921
Inventories	6,121	4,139
Investment in Regulus Therapeutics Inc.	33,622	—
Other current assets	8,727	5,415
Total current assets	423,438	360,139
Property, plant and equipment, net	91,084	96,615
Licenses, net	6,579	9,036
Patents, net	18,646	16,259
Deposits and other assets	5,939	2,845
Total assets	$ 545,686	$ 484,894

LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 10,239	$ 8,300
Accrued compensation	7,878	9,183
Accrued liabilities	15,401	18,655
Current portion of long-term obligations	4,879	3,390
Current portion of deferred contract revenue	35,925	36,584
Total current liabilities	74,322	76,112
Long-term deferred contract revenue	66,656	17,474
2¾ percent convertible senior notes	143,990	—
2⅝ percent convertible subordinated notes	—	141,448
Long-term obligations, less current portion	7,402	4,125
Long-term financing liability for leased facility	70,550	69,877
Investment in Regulus Therapeutics Inc.	—	4,424
Total liabilities	362,920	313,460
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 101,481,134 and 100,042,976 shares issued and outstanding at December 31, 2012 and 2011, respectively	102	100
Additional paid-in capital	1,077,150	1,013,592
Accumulated other comprehensive income (loss)	12,480	(770)
Accumulated deficit	(906,966)	(841,488)
Total stockholders' equity	182,766	171,434
Total liabilities and stockholders' equity	$ 545,686	$ 484,894

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except for per share amounts)

	Years Ended December 31,		
	2012	2011	2010
Revenue:			
Research and development revenue under collaborative agreements	$ 99,100	$ 96,190	$ 102,921
Licensing and royalty revenue	2,949	2,896	5,552
Total revenue	102,049	99,086	108,473
Expenses:			
Research and development	158,458	157,397	145,160
General and administrative	12,515	12,789	11,669
Total operating expenses	170,973	170,186	156,829
Loss from operations	(68,924)	(71,100)	(48,356)
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	(1,406)	(3,554)	(6,879)
Investment income	1,844	2,414	3,370
Interest expense	(21,152)	(16,732)	(13,232)
Gain (loss) on investments, net	1,465	4,182	(713)
Gain on investment in Regulus Therapeutics Inc.	18,356	—	4,651
Loss on early retirement of debt	(4,770)	—	—
Loss before income tax benefit (expense)	(74,587)	(84,790)	(61,159)
Income tax benefit (expense)	9,109	(11)	(92)
Net loss	$ (65,478)	$ (84,801)	$ (61,251)
Basic and diluted net loss per share	$ (0.65)	$ (0.85)	$ (0.62)
Shares used in computing basic and diluted net loss per share	100,576	99,656	99,143

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Years Ended December 31,		
	2012	2011	2010
Net loss	$ (65,478)	$ (84,801)	$ (61,251)
Unrealized gains (losses) on securities, net of tax	13,250	(1,719)	(1,342)
Reclassification adjustment for realized losses included in net loss	—	—	138
Comprehensive loss	$ (52,228)	$ (86,520)	$ (62,455)

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2012, 2011 and 2010
(In thousands)

	Isis Pharmaceuticals, Inc. Stockholders' Equity						
	Common stock						
Description	Shares	Amount	Additional paid in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Noncontrolling interest in Regulus	Total stockholders' equity
Balance at December 31, 2009	98,851	$ 99	$ 985,620	$ 2,153	$ (696,150)	$ 10,343	$ 302,065
Adoption of accounting standard to deconsolidate Regulus Therapeutics Inc.	—	—	(1,954)	—	714	(10,343)	(11,583)
Net loss	—	—	—	—	(61,251)	—	(61,251)
Change in unrealized gains (losses)	—	—	—	(1,342)	—	—	(1,342)
Reclassification adjustment for realized gains included in net income	—	—	—	138	—	—	138
Options exercised and employee stock purchase plan issuances	475	—	4,356	—	—	—	4,356
Warrants exercised	68	—	—	—	—	—	—
Share-based compensation expense	—	—	12,159	—	—	—	12,159
Balance at December 31, 2010	99,394	$ 99	$ 1,000,181	$ 949	$ (756,687)	$ —	$ 244,542
Net loss	—	—	—	—	(84,801)	—	(84,801)
Change in unrealized gains (losses)	—	—	—	(1,719)	—	—	(1,719)
Options exercised and employee stock purchase plan issuances	646	1	3,566	—	—	—	3,567
Warrants exercised	3	—	—	—	—	—	—
Share-based compensation expense	—	—	9,845	—	—	—	9,845
Balance at December 31, 2011	100,043	$ 100	$ 1,013,592	$ (770)	$ (841,488)	$ —	$ 171,434
Net loss	—	—	—	—	(65,478)	—	(65,478)
Change in unrealized gains (losses)	—	—	—	13,250	—	—	13,250
Options exercised and employee stock purchase plan issuances	1,438	2	9,468	—	—	—	9,470
2⅝ percent convertible subordinated notes redemption, equity portion	—	—	(12,041)	—	—	—	(12,041)
2¾ percent convertible senior notes, equity portion, net of issuance costs	—	—	57,560	—	—	—	57,560
Share-based compensation expense	—	—	8,571	—	—	—	8,571
Balance at	101,481	$ 102	$ 1,077,150	$ 12,480	$ (906,966)	$ —	$ 182,766

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2012	2011	2010
Operating activities:			
Net loss	$ (65,478)	$ (84,801)	$ (61,251)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	7,074	6,594	4,840
Amortization of patents	1,224	1,938	1,961
Amortization of licenses	2,457	3,252	2,376
Amortization of premium on investments, net	4,193	5,410	5,075
Amortization of debt issuance costs	619	507	507
Amortization of 2⅝ percent convertible subordinated notes discount	6,169	8,553	7,795
Amortization of 2¾ percent convertible subordinated notes discount	2,268	—	—
Amortization of long-term financing liability for leased facility	6,503	2,872	—
Share-based compensation expense	8,571	9,845	12,159
Equity in net loss of Regulus Therapeutics Inc.	1,406	3,554	6,879
Gain on investment in Regulus Therapeutics Inc.	(18,356)	—	(4,651)
Loss on early retirement of debt	4,770	—	—
Gain from the sale of property, plant and equipment	—	—	(72)
(Gain) loss on investments, net	(1,465)	(4,182)	713
Non-cash losses related to patents, licensing and property, plant and equipment	825	1,924	1,512
Tax benefit from other unrealized gains on securities	(9,111)	—	—
Changes in operating assets and liabilities:			
Contracts receivable	6,399	(5,679)	10,479
Inventories	(1,982)	(1,655)	284
Other current and long-term assets	279	914	(943)
Accounts payable	1,292	875	1,325
Accrued compensation	(1,305)	2,352	394
Income taxes payable	—	—	(7,178)
Deferred rent	255	382	—
Accrued liabilities	(3,254)	6,273	1,013
Deferred contract revenue	48,523	(70,857)	(46,810)
Net cash provided by (used in) operating activities	1,876	(111,929)	(63,593)
Investing activities:			
Purchases of short-term investments	(217,877)	(371,108)	(530,137)
Proceeds from the sale of short-term investments	242,659	488,918	577,533
Purchases of property, plant and equipment	(1,479)	(10,203)	(13,237)
Proceeds from the sale of property, plant and equipment	—	—	185
Proceeds from land sold to BioMed	—	—	10,147
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	—	—	(16,228)
Acquisition of licenses and other assets, net	(3,691)	(3,667)	(4,319)
Investment in Regulus Therapeutics Inc.	(3,000)	—	—
Purchases of strategic investments	(790)	(359)	(250)
Proceeds from the sale of strategic investments	2,177	4,445	—
Net cash provided by investing activities	17,999	108,026	23,694
Financing activities:			
Proceeds from issuance of equity	9,470	3,567	4,356
Proceeds from issuance of 2¾ percent convertible senior notes, net of issuance costs	194,697	—	—
Principal and premium payment on redemption of the 2⅝ percent convertible subordinated notes	(163,718)	—	—
Proceeds from equipment financing arrangement	9,100	1,625	4,694
Principal payments on debt and capital lease obligations	(10,419)	(5,864)	(4,354)
Net cash provided by (used in) financing activities	39,130	(672)	4,696
Net increase (decrease) in cash and cash equivalents	59,005	(4,575)	(35,203)
Cash and cash equivalents at beginning of year	65,477	70,052	105,255
Cash and cash equivalents at end of year	$ 124,482	$ 65,477	$ 70,052

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

Supplemental disclosures of cash flow information:			
Interest paid	$ 5,770	$ 4,804	$ 4,889
Income taxes paid, net of refund received	$ 2	$ 2	$ 7,270
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 647	$ 902	$ 922
Capital lease obligations	$ —	$ —	$ 770
Capitalized costs and financing liability associated with leased facility	$ —	$ 59,730	$ —

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. (“we”, “us” or “our”) and our wholly owned subsidiary, Symphony GenIsis, Inc., which is currently inactive. In addition to our wholly owned subsidiary, our consolidated financial statements include our equity investment in Regulus Therapeutics Inc. We used the equity method of accounting to account for our investment in Regulus Therapeutics Inc. until November 2012. In October 2012, Regulus completed an initial public offering (IPO). We now own less than 20 percent of Regulus’ common stock and we no longer have significant influence over the operating and financial policies of Regulus. As a result, in the fourth quarter of 2012, we stopped using the equity method of accounting for our equity investment in Regulus and instead we began accounting for our investment at fair value.

Organization and business activity

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. We were organized principally to develop human therapeutic drugs using antisense technology.

Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a loss from continuing operations for the years ended December 31, 2012, 2011 and 2010, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would be anti-dilutive:

- $2^{5}/_{8}$ percent convertible subordinated notes;
- $2^{3}¤_{4}$ percent convertible senior notes;
- GlaxoSmithKline convertible promissory notes issued by Regulus;
- Dilutive stock options;
- Restricted stock units; and
- Warrants issued to Symphony GenIsis Holdings LLC.

In April 2011, Symphony GenIsis Holdings LLC exercised the remaining warrants. In September 2012, we redeemed all of our $2^{5}¤_{8}$ percent convertible subordinated notes. Until the completion of Regulus’ IPO in October 2012, we were guarantors of up to $5 million plus accrued interest on the two convertible notes that Regulus issued to GlaxoSmithKline, or GSK.

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In those instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Research and development revenue under collaborative agreements

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services. Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and then accounted for as a single unit of accounting. When the delivered items in an arrangement have “stand-alone value” to our customer, we account for the deliverables as separate units of accounting and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a standalone basis. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense therapeutics against five cancer targets. As part of the collaboration, we received a $25 million upfront payment and are eligible to receive a $6 million payment in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$. We also granted AstraZeneca options to license up to three drugs under a separate research program. We are responsible for completing an ongoing clinical study of ISIS-STAT3$_{Rx}$ and IND-enabling studies for ISIS-AZ1$_{Rx}$. AstraZeneca will be responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$. In addition, if AstraZeneca exercises its option for any drugs resulting from the research program, AstraZeneca will assume global development, regulatory and commercialization responsibilities for such drug. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that certain deliverables, either individually or in combination, have stand-alone value. Below is a list of the four separate units of accounting under our agreement:

- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-STAT3$_{Rx}$ for the treatment of cancer;
- The development services we will perform for ISIS-STAT3$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AZ1$_{Rx}$ and the research services we will perform for ISIS-AZ1$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we will perform for this program.

We determined that the ISIS-STAT3$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3$_{Rx}$ is currently in development and it is possible that AstraZeneca or another third party could conduct clinical trials without assistance from us. As a result, we consider the ISIS-STAT3$_{Rx}$ license and the development services for ISIS-STAT3$_{Rx}$ to be separate units of accounting. We recognized the revenue allocated to the ISIS-STAT3$_{Rx}$ license on the date of the agreement because that is when we delivered the license. We will recognize the revenue allocated to the development services for ISIS-STAT3$_{Rx}$ over the period of time we perform services. The ISIS-AZ1$_{Rx}$ license is also an exclusive license. Because of the early stage of research for ISIS-AZ1$_{Rx}$, we believe that our knowledge and expertise with antisense technology is essential for AstraZeneca or another third party to successfully develop ISIS-AZ1$_{Rx}$. As a result, we concluded that the ISIS-AZ1$_{Rx}$ license does not have stand-alone value and we combined the ISIS-AZ1$_{Rx}$ license and related research services into one unit of accounting. We will recognize revenue for the combined unit of accounting over the period of time we perform services. We determined that the options under the research program did not have stand-alone value because AstraZeneca cannot develop or commercialize drugs resulting from the research program until AstraZeneca exercises the respective option or options. As a result, we considered the research options and the related research services as a combined unit of accounting. We will recognize revenue for the combined unit of accounting over the period of our performance.

We determined that the allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

We allocated the $25 million upfront payment based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the licenses granted for ISIS-STAT3$_{Rx}$ and ISIS-AZ1$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for each drug. We then discounted the projected income for each license to present value. The significant inputs we used to determine the projected income of the licenses included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the research and development services by using our internal estimates of the cost to perform the specific services, marked up to include a reasonable profit margin, and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform research and development. The significant inputs we used to determine the selling price of the research and development services included:

- The number of internal hours we will spend performing these services;
- The estimated number and cost of studies we will perform;
- The estimated number and cost of studies that we will contract with third parties to perform; and
- The estimated cost of drug product we will use in the studies.

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment in December 2012 for the ISIS-STAT3$_{Rx}$ license. We are recognizing the remaining $15.7 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $600,000, from the amount we recorded.

Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail.

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to

another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement.

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN_{Rx} for Spinal Muscular Atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN_{Rx} through completion of Phase 2/3 clinical trials. In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of Phase 2 clinical trials. In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets. All three of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated the SMA, DMPK, and neurology agreements to determine whether we should account for them as separate agreements or as a single multiple element arrangement. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, the first two agreements cover two different diseases while the targets for the third agreement are yet to be defined, there are no interrelated or interdependent deliverables, there are no provisions in either agreement that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all three of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective research and development term, which is the estimated period of our performance.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans. During the first step of the development stage, we or our partners study our drugs in IND-enabling studies, which are animal studies intended to support an Investigational New Drug, or IND, application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate. The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the Food and Drug Administration, or FDA, and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage. If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing approval such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.

- Marketing approval in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain approval from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with ongoing access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GSK we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam Pharmaceuticals, Inc. to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In 2012, the FDA accepted the NDA for KYNAMRO. In 2011, we initiated a Phase 1 clinical study on ISIS-TTR_{Rx}, the first drug selected as part of our collaboration with GSK and we selected ISIS-AAT_{Rx} as the second development candidate as part of that collaboration. We consider milestones related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Therefore, we recognized the entire $25 million milestone payment from Genzyme for acceptance of the NDA of KYNAMRO in 2012 and the two $5 million milestone payments from GSK in their entirety in 2011. Further information about our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Research and development expenses

We expense research and development costs as we incur them. Included in research and development expenses are costs associated with our collaboration agreements. For the years ended December 31, 2012, 2011 and 2010, research and development costs of approximately $39.0 million, $26.3 million, and $44.6 million, respectively, were related to collaborative research and development arrangements.

Concentration of credit risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. We place our cash equivalents and certain of our short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of 90 days or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive loss and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At December 31, 2012 we held ownership interests of less than 20 percent in each of the respective companies.

We account for our equity investments in publicly-held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive loss. We account for equity investments in privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. Most of the cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those circumstances we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is

temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the years ended December 31, 2012, 2011 and 2010. Total inventory, which consisted of raw materials, was $6.1 million and $4.1 million as of December 31, 2012 and 2011, respectively.

Property, plant and equipment

We carry our property, plant and equipment at cost, which consists of the following (in thousands):

	December 31,	
	2012	2011
Equipment and computer software	$ 44,109	$ 42,422
Building and building systems	48,120	48,431
Land improvements	2,849	2,822
Leasehold improvements	34,931	34,839
Furniture and fixtures	5,342	5,323
	135,351	133,837
Less accumulated depreciation	(54,465)	(47,420)
	80,886	86,417
Land	10,198	10,198
	$ 91,084	$ 96,615

We depreciate our property, plant and equipment on the straight-line method over estimated useful lives as follows:

Computer software and hardware	3 years
Manufacturing equipment	10 years
Other equipment	5-7 years
Furniture and fixtures	5-10 years
Building	40 years
Building systems and improvements	10-25 years
Land improvements	20 years

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term.

Licenses

We obtain licenses from third parties and capitalize the costs related to exclusive licenses. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately three years and 15 years. The cost of our licenses at December 31, 2012 and 2011 was $36.2 million. Accumulated amortization related to licenses was $29.6 million and $27.2 million at December 31, 2012 and 2011, respectively. Based on existing licenses, estimated amortization expense related to licenses is as follows:

Years Ending December 31,	Amortization (in millions)
2013	$ 2.0
2014	$ 1.9
2015	$ 1.9
2016	$ 0.8
2017	$ —

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs. We amortize patent costs over their useful lives, beginning with the date the United States Patent and

Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 9.9 years at December 31, 2012. In 2012, 2011 and 2010, we recorded non-cash charges of $817,000, $1.9 million and $1.5 million, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

The cost of our patents at December 31, 2012 and 2011 was $31.4 million and $29.9 million, respectively. Accumulated amortization related to patents was $12.8 million and $13.7 million at December 31, 2012 and 2011, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)
2013	$ 1.0
2014	$ 0.9
2015	$ 0.9
2016	$ 0.8
2017	$ 0.7

Fair value of financial instruments

We have estimated the fair value of our financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. We report our investment securities at their estimated fair value based on quoted market prices for identical or similar instruments.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and exclusive licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. We recorded a charge of $825,000, $1.9 million and $1.5 million for the years ended December 31, 2012, 2011 and 2010, respectively, related primarily to the write-down of intangible assets.

Equity method of accounting

We accounted for our ownership interest in Regulus using the equity method of accounting until November 2012. Under the equity method of accounting, we included our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our 2011 consolidated balance sheet, we presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." In October 2012, Regulus completed an IPO. We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As a result, we stopped using the equity method of accounting for our investment in Regulus and instead we began accounting for our investment at fair value. We also recorded an $18.4 million gain to reflect the change in our ownership percentage as a result of Regulus' IPO. In 2010, we recorded a $4.7 million gain to reflect the change in our ownership percentage due to the $10 million investment Sanofi made in Regulus.

Use of estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of December 31, 2012 and 2011, we had collaborative arrangements with six entities that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have both the power to direct the activities that most significantly impact the economic performance of our variable interest entities and the obligation to absorb losses or the right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. As of December 31, 2012, the total carrying value of our investments in variable interest entities was $38.5 million, and was primarily related to our investment in Regulus. Our maximum exposure to loss related to these variable interest entities is limited to the carrying value of our investments.

Stock-based compensation

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our Employee Stock Purchase Plan, or ESPP, based on the estimated fair value of the award on the date of grant using an option-pricing model. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We utilize the Black-Scholes model as our method of valuing option awards and stock purchase rights under the ESPP. On the grant date, we use our stock price and assumptions regarding a number of highly complex and subjective variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and

because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although we determine the estimated fair value of employee stock options using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

We recognize compensation expense for option awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

In 2012, we began granting RSUs to our employees and the Board of Directors. The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period.

See Note 5, *Stockholders' Equity,* for additional information regarding our share-based compensation plans.

Comprehensive loss

Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that we exclude from net loss including unrealized holding gains and losses, net of taxes, and reclassification adjustments for realized gains and losses on our available-for-sale securities. We display comprehensive loss and its components in our consolidated statements of comprehensive loss.

Convertible debt

In August 2012, we completed a $201.3 million offering of convertible senior notes, which mature in 2019 and bear interest at 2¾ percent. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem our 2⅝ percent convertible subordinated notes. Consistent with how we accounted for our 2⅝ percent notes, we account for our 2¾ percent notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our 2¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt instrument at a discount. We are amortizing the debt discount over the life of these 2¾ percent notes as additional non-cash interest expense utilizing the effective interest method. For additional information, see Note 4, *Long-Term Obligations and Commitments*.

Segment information

Prior to 2011, we reported our results in two separate segments: Drug Discovery and Development and Regulus. We stopped considering Regulus as an operating segment because our chief decision making officer stopped reviewing Regulus' operating results for purposes of making resource allocations. Therefore we now only operate in, and will provide financial information and results for, our Drug Discovery and Development operations.

Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and an investment in equity securities in a publicly-held biotechnology company; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of two publicly-held biotechnology companies for which we calculated a lack of marketability discount because there are restrictions on when we can trade the securities. The majority of our securities have been classified as Level 2. To estimate the fair value of securities classified as Level 2, we utilize the services of a fixed income pricing provider that uses an industry standard valuation model. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids. We validate the fair value of securities from our pricing provider by understanding the pricing model they use and comparing their assessment of the fair value of our Level 2 investments to the fair value provided by the custodians of our Level 2 investments. Our pricing provider and custodians use similar techniques to derive fair value for Level 2 securities. During the years ended December 31, 2012 and 2011 there were no transfers between our Level 1 and Level 2 investments. We use the end of reporting period method for determining transfers between levels.

As of December 31, 2012, we classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc., or Sarepta, as Level 3. We calculated a lack of marketability discount on the fair value of these investments because there are restrictions on when we can trade the securities. We consider the inputs we used to calculate the lack of marketability discount Level 3 inputs and, as a result, we categorized our investments as Level 3. We determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ends. As of December 31, 2012, the gross fair value of our investment in Regulus and Sarepta was $44.4 million and $1.0 million, respectively, and the lack of marketability discount was $10.8 million and $296,000, respectively. During the year ended December 31, 2012, our other comprehensive loss included unrealized gains of $18.1 million and $688,000, respectively, related to our investment in Regulus and Sarepta. As of December 31, 2011, we had no securities that we classified as Level 3.

We measure the following major security types at fair value on a recurring basis. We break down the inputs used to measure fair value for these assets at December 31, 2012 and 2011 as follows (in thousands):

	At December 31, 2012	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 105,496	$ 101,496	$ 4,000	$ —
Corporate debt securities (2)	193,507	—	193,507	—

Debt securities issued by U.S. government agencies (2)	18,108	—	18,108	—
Debt securities issued by the U.S. Treasury (2)	13,452	13,452	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	24,897	—	24,897	—
Investment in Regulus Therapeutics Inc.	33,622	—	—	33,622
Equity securities (3)	4,874	4,146	—	728
Total	$ 393,956	$ 119,094	$ 240,512	$ 34,350

	At December 31, 2011	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 58,892	$ 55,893	$ 2,999	$ —
Corporate debt securities (2)	166,922	—	166,922	—
Debt securities issued by U.S. government agencies (2)	80,440	—	80,440	—
Debt securities issued by the U.S. Treasury (2)	2,356	2,356	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	28,469	—	28,469	—
Equity securities (3)	1,282	1,282	—	—
Total	$ 338,361	$ 59,531	$ 278,830	$ —

(1) Included in cash and cash equivalents on our consolidated balance sheet.

(2) Included in short-term investments on our consolidated balance sheet.

(3) Included in other current assets on our consolidated balance sheet.

Income Taxes

We use the asset and liability method of accounting for income taxes. Under the asset and liability method, deferred tax assets and liabilities reflect the impact of temporary differences between amounts of assets and liabilities for financial reporting purposes and such amounts as measured under enacted tax laws. We record a valuation allowance to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that we will not recognize some or all of the deferred tax assets.

In our financial statements, we recognize the impact of an uncertain income tax position on our income tax returns at the largest amount that the relevant taxing authority is more-likely-than-not to sustain upon audit. If we feel that the likelihood of sustaining an uncertain income tax position is less than 50 percent, we do not recognize it.

Impact of recently issued accounting standards

In May 2011, the FASB amended its authoritative guidance on the measurement and disclosure for fair value measurements. The amendment clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. The guidance is effective prospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. We adopted this amendment on January 1, 2012. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In June 2011, the FASB amended its authoritative guidance on the presentation of comprehensive income. Under the amendment, companies have the option to present the components of net income and other comprehensive income either in a single continuous statement of comprehensive income or in separate but consecutive statements. This amendment eliminates the option to present the components of other comprehensive income as part of the statement of changes in stockholders' equity. The amendment does not change the items that companies must report in other comprehensive income or when companies must reclassify an item of other comprehensive income to net income. In December 2011, the FASB issued an update that defers the presentation requirement for other comprehensive income reclassifications on the face of the financial statements. The guidance is effective retrospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. We adopted this amendment on January 1, 2012. As this guidance relates to presentation only, the adoption of this guidance did not have any other effect on our consolidated financial statements.

2. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-targeting therapeutics. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, and certain early fundamental patents in the microRNA field. Alnylam made an initial investment of $10 million in Regulus to balance both companies' ownership. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner. In early 2009, Regulus raised $20 million in a Series A preferred stock financing in which we and Alnylam were the sole and equal investors in the financing.

In October 2010, Sanofi invested $10 million in Regulus. From this investment Sanofi acquired less than 10 percent ownership of Regulus, leaving us with approximately 46 percent ownership. Under the equity method of accounting, when Regulus issued shares to Sanofi, we recorded a gain of $4.7 million and adjusted the carrying value of our investment in Regulus to reflect the increased valuation of Regulus and the change in our ownership percentage.

In October 2012, Regulus completed an IPO of approximately 12.7 million shares of its common stock at $4.00 per share. As part of the offering, we purchased $3.0 million of Regulus' common stock at the offering price. Upon the close of the offering, our investment in Regulus' preferred shares converted into common stock and we received one share of Regulus' common stock for every two shares of Preferred Series A stock that we held at the date of the offering. At December 31, 2012, we owned approximately seven million shares of Regulus' common stock. We currently own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As a result, in the fourth quarter of 2012, we stopped using the equity method of accounting for our equity investment in Regulus and instead we began accounting for it at fair value which includes a lack of marketability discount because there are restrictions on when we can trade the securities. In the fourth quarter of 2012, we recorded an $18.4 million gain to reflect the change in our ownership percentage as a result of Regulus' IPO. We have reflected this gain in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc."

Summarized financial information for Regulus for the nine months ended September 30, 2012 and the years ended December 31, 2011 and 2010 and the balance sheet at December 31, 2011 is as follows (in thousands):

	Nine Months Ended September 30,	Year Ended December 31,	
	2012	2011	2010
Net revenues	$ 9,462	$ 13,789	$ 8,601
Operating expenses	17,733	20,926	24,099
Loss from operations	(8,271)	(7,137)	(15,498)
Other expense	(2,289)	(259)	(91)
Income tax benefit (expense)	28	(206)	30
Net loss	$ (10,532)	$ (7,602)	$ (15,559)

	December 31, 2011
Current assets	$ 38,666
Non-current assets	4,215
Total assets	$ 42,881
Current liabilities	$ 12,850
Non-current liabilities	28,834
Total liabilities	$ 41,684
Net assets	$ 1,197

3. Investments

As of December 31, 2012, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2012:

One year or less	56%
After one year but within two years	32%
After two years but within three years	12%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 88 percent of our available-for-sale securities having a maturity of less than two years.

At December 31, 2012, we had an ownership interest of less than 20 percent in each of three private companies and four public companies with which we conduct business. The privately-held companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen Inc., and Atlantic Pharmaceuticals Limited. The publicly-traded companies are Antisense Therapeutics Limited, or ATL, iCo Therapeutics Inc., Regulus and Sarepta. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value and record unrealized gains and losses as a separate component of comprehensive loss and include net realized gains and losses in gain (loss) on investments. In October 2012, Regulus completed an IPO and we now own less than 20 percent of Regulus' common stock. In the fourth quarter of 2012, we stopped using the equity method to account for our investment in Regulus and instead we began accounting for it at fair value. During 2011, we recognized a $4.2 million net gain on investments primarily consisting of the $4.4 million gain we recognized from our ownership interest in Excaliard Pharmaceuticals Inc. when Pfizer Inc. acquired Excaliard. During 2012, we recognized a $1.5 million net gain on investments primarily consisting of a $1.3 million gain for contingent payments we received from Pfizer, Inc. triggered by its decision to advance EXC 001 into a Phase 2 study. See further discussion about our investments in these satellite companies in Note 7, *Collaborative Arrangements and Licensing Agreements*.

The following is a summary of our investments (in thousands):

	Amortized	Unrealized	Other-Than-Temporary Impairment	Estimated

December 31, 2012	Cost	Gains	Losses	Loss	Fair Value
Short-term investments:					
Corporate debt securities	$ 113,249	$ 81	$ (9)	$ —	$ 113,321
Debt securities issued by U.S. government agencies	10,100	2	(66)	—	10,036
Debt securities issued by the U.S. Treasury	1,000	1	—	—	1,001
Debt securities issued by states of the United States and political subdivisions of the states	16,560	18	(2)	—	16,576
Total securities with a maturity of one year or less	140,909	102	(77)	—	140,934
Corporate debt securities	80,166	112	(92)	—	80,186
Debt securities issued by U.S. government agencies	8,034	38	—	—	8,072
Debt securities issued by the U.S. Treasury	12,424	27	—	—	12,451
Debt securities issued by states of the United States and political subdivisions of the states	8,306	31	(16)	—	8,321
Total securities with a maturity of more than one year	108,930	208	(108)	—	109,030
Subtotal	$ 249,839	$ 310	$ (185)	$ —	$ 249,964

December 31, 2012	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Current portion (Regulus Therapeutics Inc.)	$ 15,526	$ 18,096	$ —	$ —	$ 33,622
Current portion (included in Other current assets)	1,579	4,175	—	(880)	4,874
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 17,730	$ 22,271	$ —	$ (880)	$ 39,121
	$ 267,569	$ 22,581	$ (185)	$ (880)	$ 289,085

December 31, 2011	Amortized Cost	Unrealized Gains	Unrealized Losses	Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 109,842	$ 13	$ (255)	$ —	$ 109,600
Debt securities issued by U.S. government agencies	53,723	35	(5)	—	53,753
Debt securities issued by the U.S. Treasury	2,353	3	—	—	2,356
Debt securities issued by states of the United States and political subdivisions of the states	16,141	4	(3)	—	16,142
Total securities with a maturity of one year or less	182,059	55	(263)	—	181,851
Corporate debt securities	57,632	21	(331)	—	57,322
Debt securities issued by U.S. government agencies	26,754	—	(67)	—	26,687
Debt securities issued by states of the United States and political subdivisions of the states	12,331	19	(23)	—	12,327
Total securities with a maturity of more than one year	96,717	40	(421)	—	96,336
Subtotal	$ 278,776	$ 95	$ (684)	$ —	$ 278,187

December 31, 2011	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 624	$ —	$ (880)	$ 1,282
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 624	$ —	$ (880)	$ 1,907
	$ 280,939	$ 719	$ (684)	$ (880)	$ 280,094

Investments we consider to be temporarily impaired at December 31, 2012 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses
Corporate debt securities	39	$ 57,997	$ (101)
Debt securities issued by U.S. government agencies	1	5,029	(66)
Debt securities issued by states of the United States and political subdivisions of the states	4	9,716	(18)
Total temporarily impaired securities	44	$ 72,742	$ (185)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore we anticipate full recovery of their amortized cost basis at maturity.

4. Long-Term Obligations and Commitments

Long-term obligations consisted of the following (in thousands):

	December 31, 2012	December 31, 2011

2¾ percent convertible senior notes	$ 143,990	$ —
2⅝ percent convertible subordinated notes	—	141,448
Long-term financing liability for leased facility	70,550	69,877
Equipment financing arrangement	9,993	5,325
Leases and other obligations	2,288	2,190
Total	$ 226,821	$ 218,840
Less: current portion	(4,879)	(3,390)
Total Long-Term Obligations	$ 221,942	$ 215,450

Convertible Notes

In August 2012, we completed a $201.3 million convertible debt offering, which raised net proceeds of $194.7 million, after deducting $6.6 million in issuance costs. The $201.3 million convertible senior notes mature in 2019 and bear interest at 2¾ percent, which is payable semi-annually in arrears on April 1 and October 1 of each year. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem the entire $162.5 million in principal of our 2⅝ percent notes at a price of $164.0 million including accrued interest. The $162.5 million convertible subordinated notes had a maturity date of 2027 and bore interest at 2⅝ percent, which was payable in cash semi-annually. We recognized a $4.8 million loss as a result of the redemption of the 2⅝ percent notes. A significant portion of the loss, or $3.6 million, was non-cash and related to the unamortized debt discount and debt issuance costs and the remainder was related to a $1.2 million early redemption premium we paid to the holders of the 2⅝ percent notes.

The 2¾ percent notes are convertible at the option of the note holders prior to July 1, 2019 only under certain conditions. On or after July 1, 2019, the notes are initially convertible into approximately 12.1 million shares of common stock at a conversion price of approximately $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing these notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

We did not include the potential effect of the conversion of our convertible notes into our common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

We account for our convertible notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of similar debt instruments without the conversion feature, which results in us recording our convertible debt at a discount. We amortize the resulting debt discount as additional non-cash interest expense over the expected life of the debt, or seven years, for both our 2¾ percent notes and 2⅝ percent notes. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate was eight percent and 9.3 percent for the 2¾ percent notes and 2⅝ percent notes, respectively. At December 31, 2012 the principal and accrued interest payable on the 2¾ percent notes was $202.6 million and the fair value based on quoted market prices was $198.7 million. Interest expense for the year ended December 31, 2012, 2011 and 2010 included $8.4 million, $8.6 million and $7.8 million, respectively, of non-cash interest expense related to the amortization of the debt discount for our convertible notes.

The following table summarizes information about the equity and liability components of the 2¾ percent and 2⅝ percent notes, (in thousands):

	December 31,	
	2012	2011
	2¾ percent notes	2⅝ percent notes
Principal amount of convertible notes outstanding	$ 201,250	$ 162,500
Unamortized portion of liability component	(57,260)	(21,052)
Long-term debt	$ 143,990	$ 141,448
Carrying value of equity component	$ 59,528	$ 54,640

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent. As of December 31, 2012, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.57 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at December 31, 2012 and 2011 was $10.0 million and $5.3 million, respectively.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2012 are as follows (in thousands):

2013	$ 10,824
2014	9,351
2015	7,648

2016		5,594
2017		5,594
Thereafter		213,400
Subtotal	$	252,411
Less: current portion		(4,879)
Less: fixed and determinable interest		(40,310)
Less: debt discount		(57,260)
Deferred rent		1,430
Total	$	151,392

Operating Leases

We lease certain office equipment as well as office and laboratory space under non-cancelable operating leases with terms through December 2031. We are located in three buildings in Carlsbad, California and occupy approximately 231,000 square feet of laboratory and office space. Our facilities include a 176,000 square foot facility that we use for our primary research and development activities, a 28,704 square foot manufacturing facility and a 25,792 square foot building adjacent to our manufacturing facility. Our 28,704 square foot facility houses manufacturing suites for our drug development business built to meet current Good Manufacturing Practices and our 25,792 square foot facility has laboratory and office space that we use to support our manufacturing activities. We account for the lease of our 176,000 square foot facility as a financing obligation as discussed below. The lease for our 28,704 square foot manufacturing facility expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. The lease for the 25,792 square foot facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods.

Annual future minimum payments under operating leases as of December 31, 2012 are as follows (in thousands):

		Operating Leases
2013	$	1,423
2014		1,389
2015		1,332
2016		1,380
2017		1,401
Thereafter		20,578
Total minimum payments	$	27,503

Rent expense for the years ended December 31, 2012, 2011 and 2010 was $1.9 million, $4.6 million and $4.3 million, respectively. In connection with certain of our leases, we recognize rent expense on a straight line basis over the lease term resulting in a deferred rent balance of $1.4 million and $1.2 million at December 31, 2012 and 2011, respectively.

Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed our primary research and development facility in Carlsbad, California. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, we recorded the costs for the facility as a fixed asset and we also recorded a corresponding liability in our non-current liabilities as a long-term financing obligation. In July 2011, we took possession of the facility. In the third quarter of 2011, we began depreciating the cost of the facility over its economic useful life. At December 31, 2012 and 2011, the facility and associated parcel of land had a net book value of $68.9 million and $71.5 million, respectively, which included $3.2 million and $945,000, respectively, of accumulated depreciation. We will apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In conjunction with the lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land, which requires us to account for the purchase and sale of the land as a financing transaction. As such, our property, plant and equipment at December 31, 2012 and 2011 included the value of the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease terminates.

The lease on our primary research and development facility expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility and land at the end of each year from 2016 through 2020, and at the end of 2026 and 2031.

Annual future rent payments as of December 31, 2012 for our primary research and development facility are as follows (in thousands):

		Future Rent Payments
2013	$	5,829
2014		6,179
2015		6,179
2016		6,550
2017		6,550
Thereafter		112,451
Total minimum payments	$	143,738

5. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2012, there were no shares of our Series A Convertible Exchangeable five percent Preferred Stock or Series B Convertible Exchangeable five percent Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2012.

Common Stock

At December 31, 2012 and 2011, we had 200,000,000 shares of common stock authorized, of which 101,481,134 and 100,042,976 were issued and outstanding, respectively. As of December 31, 2012, total common shares reserved for future issuance were 23,114,372.

We issued 1,438,000, 646,000 and 475,000 shares of common stock for stock option exercises and the Employee Stock Purchase Plan ("ESPP") purchases during the years ending December 31, 2012, 2011 and 2010, respectively. We received net proceeds from these transactions of $9.5 million, $3.6 million and $4.4 million in 2012, 2011 and 2010, respectively.

Stock Option Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options we granted after May 26, 2004 have a term of seven years while options we granted before May 26, 2004 have a term of ten years. At December 31, 2012, a total of 8,105,367 options were outstanding, of which options to purchase 4,972,040 shares were exercisable, and 1,747,698 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which, as amended, provided for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. At December 31, 2012, a total of 2,116,621 options were outstanding, of which 2,077,357 shares were exercisable, and no shares were available for future grant under the 2000 Plan. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

With respect to both the 1989 Plan and 2000 Plan, in the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan and the 1989 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan and the 1989 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan and the 1989 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards. The plan provides for the purchase of up to 2,000,000 shares of our common stock for issuance to our employees, directors, and consultants. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock units awards to our employees, directors and consultants. Under the 2011 Plan, stock options cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years. We granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four year period. At December 31, 2012, a total of 182,353 options were outstanding, no shares were exercisable, and 1,817,647 shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issue to our chief executive officer and chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan.

Corporate Transactions and Change in Control under 2011 Plan

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"). The 2002 Plan provides for the purchase of up to 1,200,000 shares of our common stock to our non-employee directors. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2012, a total of 607,500 options were outstanding, 432,500 of the shares issued were exercisable and 367,000 shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the 2000 ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 2,274,596 million shares authorized in the plan as of December 31, 2012. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase beginning with the offering ending in January 1, 2010. During 2012, employees purchased and we issued to employees 124,001 shares under the ESPP at $6.13 per share. At December 31, 2012, 217,087 shares were available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2012 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2011	10,722	$ 11.39		
Granted	1,775	$ 7.92		
Exercised	(1,287)	$ 6.74		
Cancelled/forfeited/expired	(387)	$ 13.43		
Outstanding at December 31, 2012	10,823	$ 11.30	3.65	$ 9,194
Exercisable at December 31, 2012	7,482	$ 12.27	2.78	$ 3,712

The weighted-average estimated fair values of options granted were $3.55, $4.85 and $5.53 for the years ended December 31, 2012, 2011 and 2010, respectively. The total intrinsic value of options exercised during the years ended December 31, 2012, 2011 and 2010 were $7.6 million, $686,000 and $905,000, respectively, which we determined as of the date of exercise. The amounts of cash received from the exercise of stock options were $8.7 million, $2.8 million and $3.3 million for the years ended December 31, 2012, 2011 and 2010, respectively. For the year ended December 31, 2012, the weighted-average fair value of options exercised was $12.61. As of December 31, 2012, total unrecognized compensation cost related to non-vested stock-based compensation plans was $5.5 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.1 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2012 (in thousands, except per share data):

	Number of	Weighted

	Shares	Average Grant Date Fair Value Per Share
Non-vested at December 31, 2011	—	$ —
Granted	193	$ 8.37
Vested	—	$ —
Cancelled/forfeited	(5)	$ 8.42
Non-vested at December 31, 2012	188	$ 8.37

The weighted-average grant date fair value of RSUs granted to employees and the Board of Directors for the twelve months ended December 31, 2012 was $8.22 and $12.94 per RSU, respectively. As of December 31, 2012, total unrecognized compensation cost related to RSUs was $1.3 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 3.1 years.

Stock-based Valuation and Compensation Expense Information

The following table summarizes stock-based compensation expense for the year ended December 31, 2012, 2011 and 2010 (in thousands), which was allocated as follows:

	Year Ended December 31,		
	2012	2011	2010
Research and development	$ 7,246	$ 8,527	$ 10,148
General and administrative	1,325	1,318	2,011
Total	$ 8,571	$ 9,845	$ 12,159

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under the ESPP at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period. We value RSUs based on the market price of our common stock on the date of grant.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under the ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. We recognize compensation expense for stock options granted, RSUs, and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

For the years ended December 31, 2012, 2011 and 2010, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2012	2011	2010
Risk-free interest rate	1.1%	2.3%	2.7%
Dividend yield	0.0%	0.0%	0.0%
Volatility	50.7%	52.4%	55.5%
Expected life	5.1 years	5.3 years	5.1 years

Board of Director Stock Options:

	December 31,		
	2012	2011	2010
Risk-free interest rate	1.3%	2.9%	2.7%
Dividend yield	0.0%	0.0%	0.0%
Volatility	51.3%	52.8%	57.7%
Expected life	7.6 years	7.8 years	7.8 years

ESPP:

	December 31,		
	2012	2011	2010
Risk-free interest rate	0.1%	0.1%	0.2%
Dividend yield	0.0%	0.0%	0.0%
Volatility	44.5%	34.9%	47.8%
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. For the 2002 Plan, we estimated the expected term of options we have granted based on historical exercise patterns. For the 1989 Plan and 2000 Plan, we estimated the expected term of options granted subsequent to January 1, 2008, based on historical exercise patterns. The expected term for stock options we have granted prior to January 1, 2008 was a derived output of the simplified method.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

Warrants

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. In April 2011, Symphony GenIsis Holdings LLC exercised the remaining warrants.

6. Income Taxes

We have net deferred tax assets relating primarily to net operating loss carryforwards, or NOL's, and research and development tax credit carryfowards. Subject to certain limitations, we may use these deferred tax assets to offset taxable income in future periods. Since we have a history of losses and the likelihood of future profitability is not assured, we have provided a full valuation allowance for the deferred tax assets in our balance sheet as of December 31, 2012. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to increase their recorded value and a corresponding adjustment to increase income or additional paid in capital, as appropriate, in that same period.

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During 2012, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. As a result, we recorded a $9.1 million tax benefit in continuing operations and a $9.1 million tax expense in other comprehensive income for the year ended December 31, 2012.

We are subject to taxation in the United States and various state jurisdictions. Our tax years for 1994 and forward are subject to examination by the U.S. tax authorities and our tax years for 1989 and forward are subject to examination by the California tax authorities due to the carryforward of unutilized net operating losses and research and development credits. Our tax years for 2006 and 2007 are currently being audited by California's Franchise Tax Board, or FTB. We do not expect that the results of these examinations will have a material effect on our financial condition or results of operations. In 2012, the California FTB completed its audit of our 2001 and 2002 tax years, which did not result in a material adjustment on our financial statements.

The provision for income taxes on income from continuing operations were as follows (in thousands):

	Year Ended December 31,		
	2012	2011	2010
Current:			
Federal	$ —	$ —	$ (73)
State	2	11	165
Total current	2	11	92
Deferred:			
Federal	(7,827)	—	—
State	(1,284)	—	—
Foreign	—	—	—
Total deferred	(9,111)	—	—
Income Tax Expense (Benefit)	$ (9,109)	$ 11	$ 92

The reconciliation between the Company's effective tax rate on income from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Year Ended December 31,					
	2012		2011		2010	
Pre tax loss	$ (74,587)		$ (84,790)		$ (61,251)	
Statutory rate	(26,105)	35.0%	(29,677)	35.0%	(21,438)	35.0%
State income tax net of federal benefit	(4,284)	5.7%	(4,870)	5.7%	(3,518)	5.7%
Net change in valuation allowance	25,269	(33.9)%	41,136	(48.5)%	26,869	(43.9)%
Gain on Investment in Regulus Therapeutics, Inc.	(6,353)	8.5%	—	—	—	—
Tax credits	806	(1.1)%	(4,202)	5.0%	(3,175)	5.2%
Noncontrolling interest	—	—	1,448	(1.7)%	908	(1.5)%
Deferred tax true-up	839	(1.1)%	(4,236)	5.0	—	—

Other	719	(0.9)%	412	(0.5)%	446	(0.7)%
Effective rate	$ (9,109)	12.2%	$ 11	(0.0)%	$ 92	(0.2)%

Significant components of our deferred tax assets and liabilities as of December 31, 2012 and 2011 are as follows (in thousands):

	Year Ended December 31,	
	2012	2011
Deferred Tax Assets:		
Net operating loss carryovers	$ 244,539	$ 195,399
R&D credits	46,928	44,970
Capitalized R&D	22,223	23,212
Deferred revenue	7,285	20,541
Accrued restructuring	3,605	10,888
Other	18,931	25,606
Total deferred tax assets	$ 343,511	$ 320,616
Deferred Tax Liabilities:		
Convertible debt	$ (23,322)	$ (9,426)
Intangible and capital assets	(6,784)	(3,702)
Net deferred tax asset	$ 313,405	$ 307,488
Valuation allowance	(313,405)	(307,488)
Net deferreds	$ —	$ —

The deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2012 and 2011 that arose directly from (or the use of which was postponed by) tax deductions related to equity compensation in excess of compensation recognized for financial reporting. Those deferred tax assets include non-qualified stock options and incentive stock options we issued. We will increase stockholders' equity by approximately $10.6 million if and when we ultimately realize such deferred tax assets. We use tax return ordering for purposes of determining when excess tax benefits have been realized.

At December 31, 2012, we had federal and California tax net operating loss carryforwards of approximately $636.9 million and $561.2 million, respectively. The Federal and California tax loss carryforwards will expire at various dates starting in 2014, unless we use them before then. We also have federal and California research and development tax credit carryforwards of approximately $44.2 million and $18.4 million, respectively. The Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless we use them prior to expiration. The California research and development tax credit carryforwards are available indefinitely. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and the shorter carryforward periods related to the state loss carryforwards.

We analyze filing positions in all of the federal and state jurisdictions where we are required to file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of being sustained.

The following table summarizes the gross amounts of unrecognized tax benefits without regard to reduction in tax liabilities or additions to deferred tax assets and liabilities if such unrecognized tax benefits were settled.

Reconciliation of unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2012	2011	2010
Beginning balance of unrecognized tax benefits	$ 9,834	$ 8,968	$ —
Decrease for prior period tax positions	(174)	(97)	—
Increase for prior period tax positions	791	—	8,231
Increase for current period tax positions	421	963	737
Ending balance of unrecognized tax benefits	$ 10,872	$ 9,834	$ 8,968

The balance of unrecognized tax benefits at December 31, 2012 of $10.9 million are tax benefits that, if we recognize them, would not impact our effective tax rates as long as they remain subject to a full valuation allowance. At December 31, 2012, there was no effect on the deferred tax assets and corresponding valuation allowance resulting from unrecognized tax benefits. We have not recognized any accrued interest and penalties related to unrecognized tax benefits during the year ended December 31, 2012 due to our NOL and research credit carryforwards. We do not foresee any material changes to unrecognized tax benefits within the next twelve months. We recognize interest and/or penalties related to income tax matters in income tax expense.

The American Taxpayer Relief Act of 2012, which reinstated the United States federal research and development tax credit retroactively from January 1, 2012 through December 31, 2013, was not enacted into law until the first quarter of 2013. Therefore, the expected tax benefit resulting from such reinstatement for 2012 will not be reflected in the Company's estimated annual effective tax rate until 2013.

7. Collaborative Arrangements and Licensing Agreements

Pharmaceutical Alliances and Licensing

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. The agreement includes $31 million in upfront and near-term payments, comprising a $25 million payment we received in December 2012 and a $6 million payment we are eligible to receive in the second quarter of 2013 assuming the research program is continuing. We are also eligible to receive milestone payments, license fees and double-digit royalties on any product sales of drugs resulting from this collaboration. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ for the treatment of cancer and a preclinical program, ISIS-AZ1$_{Rx}$, and an option to license up to three drugs we expect to develop under a separate research program.

We are currently conducting a focused clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced cancer. We are responsible for completing the ongoing clinical study and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. We have the potential to receive up to $75 million in milestone payments over the next two years, including the potential to receive up to a $50 million milestone payment subject to meeting pre-agreed efficacy and safety criteria in the ongoing ISIS-STAT3$_{Rx}$ study. If AstraZeneca successfully develops drugs under all three programs, we could receive substantive milestone payments of more than $980 million, including up to $325.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We will earn the next milestone payment of $10 million if AstraZeneca accepts ISIS-AZ1$_{Rx}$ as the second development candidate in our collaboration.

During 2012, we earned revenue of $9.3 million from the $25 million upfront payment we received from AstraZeneca in December 2012, which represented nine percent of our total revenue for that period. Our balance sheet at December 31, 2012 included deferred revenue of $15.7 million related to our relationship with AstraZeneca.

Biogen Idec

We have established three strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise. In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million in substantive milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing. We are responsible for developing ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We are also eligible receive up to $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of ISIS-SMN$_{Rx}$. We will earn the next milestone payment of $18 million if we initiate the Phase 2/3 study for ISIS-SMN$_{Rx}$.

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. Under the terms of the agreement, we received an upfront payment of $12 million and are eligible to receive up to $59 million in substantive milestone payments associated with the development of the DMPK-targeting drug prior to licensing. We are responsible for global development of the drug through the completion of Phase 2 clinical trials. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. We are also eligible to receive up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for our DMPK program.

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million and are eligible to receive development milestone payments to support research and development of each program including a $10 million milestone payment per program upon initiation of an IND-enabling toxicology study. We are also eligible to receive up to another $200 million in a license fee and regulatory milestone payments per program including up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

During 2012, we earned revenue of $8.5 million from our relationships with Biogen Idec, which represented eight percent of our total revenue for that period. Our balance sheet at December 31, 2012 included deferred revenue of $62.6 million related to the upfront payments.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. In addition to the $15 million upfront fee, we earned $8 million in milestone payments related to the development of BMS-PCSK9$_{Rx}$. The collaboration ended in December 2011, and we regained the rights to discover and develop antisense drugs to target PCSK9.

During 2012, 2011 and 2010, we earned revenue of $290,000, $2.4 million and $12.2 million, respectively, from Bristol-Myers Squibb, which represented less than one percent, two percent and 11 percent, respectively, of our total revenue for those years. Our balance sheets at both December 31, 2012 and 2011 included deferred revenue of $126,000 related to our relationship with Bristol-Myers Squibb.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin, and LY2275796, an antisense inhibitor of eIF-4E, or eukaryotic

initiation factor-4E. In the second quarter of 2012, Eli Lilly and Company decided not to continue the development of LY2181308. Therefore we will not earn future milestone payments from Eli Lilly and Company associated with LY2181308.

In December 2009, we reacquired LY2275796, which we renamed ISIS-EIF4E$_{Rx}$, and we are continuing to develop the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development. However, if we publicly disclose the results from a Phase 2 clinical study of ISIS-EIF4E$_{Rx}$:

- Eli Lilly and Company may license ISIS-EIF4E$_{Rx}$ on the predefined terms;
- Eli Lilly and Company may tell us it is not interested in licensing ISIS-EIF4E$_{Rx}$, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner; or
- Eli Lilly and Company may offer to license ISIS-EIF4E$_{Rx}$ on terms that are lower than the predefined terms, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2012, 2011 and 2010, we did not earn any revenue from our relationship with Eli Lilly and Company.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of KYNAMRO. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to KYNAMRO, including the key product related patents and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apo-B by binding to the messenger RNA, or mRNA, encoding apo-B, throughout the world.

The transaction included a $175 million licensing fee, a $150 million equity investment in our stock in which we issued Genzyme five million shares of our common stock, and a share of worldwide profits on KYNAMRO and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. In May 2012, we earned a $25 million milestone payment from Genzyme when the FDA accepted the NDA for KYNAMRO and in January 2013 we earned an additional $25 million milestone payment when the NDA was approved. We may also receive over $1.5 billion in substantive milestone payments if Genzyme achieves pre-specified events, including up to $700 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could earn under our agreement with Genzyme is $25 million upon the earlier of an NDA Approval for the use of KYNAMRO to treat patients who have heterozygous FH or annual net revenue equals or exceeds $250 million in a calendar year.

Under this alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. We agreed to supply the drug substance for KYNAMRO for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for KYNAMRO, including the initial commercial launch supply, and Genzyme will be responsible for the long term supply of KYNAMRO drug substance and finished drug product. As part of the agreement, we contributed the first $125 million in funding for the development costs of KYNAMRO. In 2011, we satisfied our development funding obligation. As such, we and Genzyme shared development expenses equally in 2012. Our shared funding of development expenses will end when KYNAMRO is profitable.

The license and co-development agreement for KYNAMRO will continue in perpetuity unless we or Genzyme terminate it earlier under the following situations:

- Genzyme may terminate the license and co-development agreement at any time by providing written notice to Isis;
- We may terminate the license and co-development agreement on a country-by-country basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize KYNAMRO in the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and Canada; and
- Either we or Genzyme may terminate the license and co-development agreement upon the other party's uncured failure to perform a material obligation under the agreement.

Upon termination of the license and co-development agreement, the license we granted to Genzyme for KYNAMRO will terminate and Genzyme will stop selling the product. In addition, if Genzyme voluntarily terminates the agreement or we terminate the agreement in a country or countries for Genzyme's failure to develop and commercialize KYNAMRO, then the rights to KYNAMRO will revert back to us and we may develop and commercialize KYNAMRO in the countries that are the subject of the termination, subject to a royalty payable to Genzyme.

If we are the subject of an acquisition, then within 180 days following the acquisition, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO license and co-development agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm.

Genzyme has agreed to monthly limits on the number of shares it can sell of the Company's stock that it purchased in February 2008. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the KYNAMRO license and co-development agreement or the date Genzyme holds less than two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During 2012, 2011 and 2010, we earned revenue of $67.6 million, $72.3 million and $66.9 million, respectively, from our relationship with Genzyme, which represented 66 percent, 73 percent and 62 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2012 and 2011 included deferred revenue of $3.8 million and $27.7 million, respectively, related to our relationship with Genzyme.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, which covers up to six programs, in which we use our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate rapid development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development.

Under the terms of the original agreement, which includes five programs in addition to the transthyretin, or TTR, program, we are eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, and we received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTR_{Rx}. We have already received $17.5 million in milestone payments from GSK related to the development of ISIS-TTR_{Rx}, including the $7.5 million milestone payment we received in February 2013. We are also eligible to earn an additional $50 million in pre-licensing milestone payments associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, GSK has increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} achieve registration and meet certain sales thresholds.

Under the terms of the amended agreement, if GSK successfully develops all six programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $231.5 million for the achievement of development milestones, up to $594.5 million for the achievement of regulatory milestones and up to $545 million for the achievement of commercialization milestones. We will earn the next milestone payment of $2 million upon dosing the 10th patient in the Phase 2/3 clinical study for ISIS-TTR_{Rx}. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During 2012, 2011 and 2010, we earned revenue of $8.2 million, $17.7 million and $10.3 million, respectively, from our relationship with GSK, which represented eight percent, 18 percent and nine percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2012 and 2011 included deferred revenue of $19.9 million and $25.3 million, respectively, related to the upfront and expansion payments.

Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively outlicensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides Achaogen developed. Aminoglycosides are a class of small molecule antibiotics that inhibit bacterial protein synthesis and that physicians use to treat serious bacterial infections. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli. The compound has also demonstrated activity against methicillin-resistant staphylococcus aureus, or MRSA.

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have received $3 million from Achaogen, $500,000 which was in Achaogen securities, as Achaogen has advanced plazomicin in development. In addition, assuming Achaogen successfully develops and commercializes the first two drugs under our agreement, we may receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We are eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin. During 2012 and 2011, we did not earn any revenue from our relationship with Achaogen. During 2010, we earned $2 million in revenue from our relationship with Achaogen, which does not include any revenue from the equity we received from Achaogen. At December 31, 2012 and 2011, we owned less than 10 percent of Achaogen's equity.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. We will earn the next milestone payment of $750,000 if Alnylam initiates a Phase 3 study for TTR. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize ssRNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay if we achieve specified development and regulatory events. As of December 31, 2012, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-targeting drug discovery.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of ssRNAi technology. Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million plus $2.6 million of research and development funding in 2009 and 2010. In November 2010, Alnylam terminated the ssRNAi research program and we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. As a result, any licenses to ssRNAi products we granted to Alnylam under the agreement, and any of Alnylam's obligations to pay milestone payments, royalties or sublicense payments to us for ssRNAi

products under the agreement, terminated. We continue to advance the development of ssRNAi technology and during the course of the collaboration, we made improvements in the activity of ssRNAi compounds, including increased efficacy and potency and enhanced distribution.

In 2012, we earned $2.7 million in sublicense revenue when Alnylam licensed our technology to Monsanto Company and Genzyme. In addition, we have the potential to receive a portion of future milestone payments and royalty payments from these licenses. As of December 31, 2012, we have earned a total of $48.1 million from Alnylam resulting from licenses of our technology for the development of RNAi therapeutics and technology that we granted to Alnylam and Alnylam has granted to its partners. During 2012, 2011 and 2010, we earned revenue from our relationship with Alnylam totaling $2.7 million, $375,000 and $10.3 million, respectively, which represented three percent, less than one percent and nine percent, respectively, of our total revenue for those years.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL1102 to Teva Pharmaceutical Industries Ltd. From early 2008 until early 2010, when Teva terminated the licensing agreement for ATL1102, we earned $3.4 million as Teva advanced the development of ATL1102. In March 2010, Teva terminated the licensing agreement for ATL1102 and returned rights to the drug to ATL.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. Over the last three years, ATL has raised approximately $8 million that it is using to advance ATL1103. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009, we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

At December 31, 2012 and 2011, we owned less than 10 percent of ATL's equity. During 2012, we did not earn any revenue from our relationship with ATL. During 2011 and 2010, we earned revenue of $210,000, and $35,000, respectively, from our relationship with ATL.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In September 2010, we participated in Atlantic Pharmaceuticals' financing by agreeing to sell to Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. At December 31, 2012 and 2011, we owned approximately 11 percent of Atlantic Pharmaceuticals' equity. Because realization of the upfront equity payment is uncertain, we recorded a full valuation allowance.

Under the agreement, we could receive substantive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $600,000 if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international Named Patient Supply regulations for patients with inflammatory bowel disease, or IBD, for which we are receiving royalties. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen. During 2012, we earned $3,000 from our relationship with Atlantic Pharmaceuticals and during 2011 and 2010 we did not earn any revenue from our relationship with Atlantic Pharmaceuticals.

Excaliard Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.

In November 2007, we entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring. We granted Excaliard an exclusive worldwide license for the development and commercialization of certain antisense drugs. Excaliard made an upfront payment to us in the form of equity and paid us $1 million in cash for the licensing of an antisense oligonucleotide drug targeting expression of connective tissue growth factor, or CTGF, that is activated during skin scarring following the wound healing process.

In December 2011, Pfizer Inc. acquired Excaliard. To date, we have received $5.7 million and we are eligible to receive up to an additional $8.3 million in contingent payments upon achievement of various milestones associated with the clinical and commercial progress of EXC 001. In addition, we continue to be eligible for milestone and royalty payments under our licensing agreement for EXC 001. Assuming Pfizer Inc. successfully develops and commercializes EXC 001, we may receive substantive milestone payments totaling up to $47.7 million for the achievement of key development and regulatory milestones, including up to $7.7 million for the achievement of development milestones and up to $40 million for the achievement of regulatory milestones. We will earn the next milestone payment of $1.5 million upon initiation of a Phase 3 study for EXC 001. We are eligible to receive royalties on any product sales of EXC 001.

At December 31, 2012, we owned no equity in Excaliard. During 2012 and 2011, we received $1.3 million and $4.4 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard, which we recorded as a gain on investments. We did not earn any revenue during 2012 and 2011 and during 2010 we earned revenue of $3,000 from our relationship with Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007. iCo is developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy and is currently evaluating it in a Phase 2 study in patients with diabetic retinopathy. We received a $500,000 upfront fee from iCo and may receive substantive milestone payments totaling up to $48.4 million for the achievement of development and regulatory milestones for multiple indications, including up to $7.9 million for the achievement of development milestones and up to $40.5 million for the achievement of regulatory milestones. We will receive the next milestone payment of $4 million if iCo initiates a Phase 3 study for iCo-007. In addition, we are eligible to receive royalties on any product sales of iCo-007. Under the terms of the agreement, iCo is solely responsible for the development and commercialization of the drug. Over the course of our relationship, iCo has paid us in a combination of cash, common stock and convertible notes. As a result, our ownership in iCo at December 31, 2012 and 2011 was approximately nine

percent and 12 percent, respectively. During 2012 we did not earn any revenue from our relationship with iCo and during 2011 and 2010 we earned $7,000 in each period from our relationship with iCo.

OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc.

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize custirsen, formerly OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely responsible for the costs, development and commercialization of custirsen. In exchange, OncoGenex agreed to pay us royalties on sales of custirsen and to share consideration it receives from licensing custirsen to a third party, except for consideration OncoGenex receives for the fair market value of equity and reimbursement of research and development expenses.

Under the amended agreement, we assigned to OncoGenex our rights in the patents claiming the composition and therapeutic methods of using custirsen and granted OncoGenex a worldwide, nonexclusive license to our know-how and patents covering our core antisense technology and manufacturing technology solely for use with custirsen. The key product-related patent that we assigned to OncoGenex was U.S. Patent number 6,900,187 having an expiration date of at least 2020; and the key core antisense technology patents we licensed OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026 and its foreign equivalents pending in Australia, Canada, the European Patent Convention and Japan. In addition, we agreed that so long as OncoGenex or its

commercialization partner is using commercially reasonable efforts to develop and commercialize custirsen, we will not research, develop or commercialize an antisense compound designed to modulate clusterin. The amended agreement will continue until OncoGenex or its commercialization partner is no longer developing or commercializing custirsen or until we terminate the agreement for OncoGenex's uncured failure to make a payment required under the agreement.

In December 2009, OncoGenex granted Teva the exclusive worldwide right and license to develop and commercialize any products containing custirsen and related compounds, with OncoGenex having an option to co-promote custirsen in the United States and Canada, for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in payments OncoGenex may receive from Teva in addition to royalties on any product sales of custirsen ranging between 3.88 percent and seven percent. Under the agreement, this royalty is due on a country- by-country basis until the later of ten years following the first commercial sale of custirsen in the relevant country, and the expiration of the last patent we assigned or licensed to OncoGenex that covers the making, using or selling of custirsen in such country.

To facilitate the execution and performance of OncoGenex's agreement with Teva, we and OncoGenex amended our license agreement primarily to give Teva the ability to cure any future potential breach by OncoGenex under our agreement. As part of this amendment, OncoGenex agreed that if OncoGenex is the subject of a change of control with a third party, where the surviving entity immediately following such change of control has the right to develop and sell custirsen, then a payment of $20 million will be due and payable to us 21 days following the first commercial sale of the product in the United States. Any non-royalty payments OncoGenex previously paid to us are creditable towards the $20 million payment, so as a result of the $10 million payment we received from OncoGenex related to its license to Teva, the remaining amount owing in the event of a change of control as discussed above is a maximum of $10 million.

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us substantive milestone payments totaling up to $3.5 million for the achievement of development and regulatory milestones, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225. As of December 31, 2012, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $500,000 if OncoGenex initiates a Phase 2 study for OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex will pay us substantive milestone payments totaling up to $5.8 million for the achievement of key development and regulatory milestones, including up to $1.3 million for the achievement of development milestones and up to $4.5 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of the drug. In January 2011, we earned a $750,000 milestone payment related to OncoGenex's Phase 2 trial in men with metastatic prostate cancer. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for OGX-427.

During 2011, we earned $750,000 in revenue from our relationship with OncoGenex. During 2012 and 2010, we did not earn any revenue from our relationship with OncoGenex.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-targeting therapeutics. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner.

We and Alnylam co-founded Regulus and we each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, and certain early fundamental patents in the microRNA field. Under this agreement, we are eligible to receive fees and/or royalty payments on microRNA therapeutic products that Regulus or its partners develop. In October 2012 Regulus completed an IPO, in which we participated by purchasing $3 million of Regulus' common stock at the offering price. We remain a significant shareholder with approximately seven million shares. We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. In the

fourth quarter of 2012 we stopped using the equity method of accounting for our investment in Regulus and instead we began accounting for our investment at fair value. In the fourth quarter of 2012, we recorded an $18.4 million gain to reflect the change in our ownership percentage as a result of Regulus' IPO.

Regulus has successfully developed strategic partnerships with partners like Sanofi, GSK, Biogen Idec and AstraZeneca. We benefit from Regulus' strategic partnerships because we have the potential to receive a portion of future milestone payments and royalty payments. For example, under Regulus' strategic partnership with Sanofi, we and Alnylam each received 7.5 percent, or $1.9 million, of the $25 million upfront payment and are eligible to receive 7.5 percent of all future milestone payments, in addition to royalties on any product sales. During 2012 and 2011, we did not earn any revenue from our relationship with Regulus. In 2010, we earned $1.9 million from our relationship with Regulus.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and physicians associate a wide variety of conditions including infection, cancer and chronic inflammation with AI. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In May 2012, Xenon selected XEN701, a drug targeting the hepcidin-hemojuvelin pathway, as a development candidate. Xenon may take an exclusive license for the development and worldwide commercialization of XEN701. Under our collaboration agreement with Xenon we may receive up to $296 million in substantive milestone payments for the achievement of pre-specified milestone events that are met by two independent products, including up to $26 million for the achievement of development milestones, up to $150 million for the achievement of regulatory milestones and up to $120 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of XEN701 and a portion of sublicense revenue. We will earn the next milestone payment of $3 million if Xenon initiates a Phase 2 clinical trial for XEN701.

In August 2012, we and Xenon entered into a separate collaboration to discover and develop an antisense drug targeting sodium channel, voltage-gated, type IX, alpha subunit, or SCN9A. Under our collaboration, we obtained exclusive and non-exclusive licenses to certain Xenon patent rights related to SCN9A. Xenon has the option to license a drug targeting SCN9A through identification of a development candidate. If Xenon exercises its option, Xenon will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. In addition to a license fee, we may receive up to $177 million in substantive milestone payments upon the achievement of pre-specified events, including up to $22 million for the achievement of development milestones, up to $85 million for the achievement of regulatory milestones and up to $70 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of SCN9A and a portion of sublicense revenue. We will earn the next milestone payment of $5 million when Xenon completes studies that are sufficient to support filing an IND for an antisense drug targeting the SCN9A gene.

During 2012 and 2011, we earned revenue of $84,000 and $80,000, respectively, from our relationship with Xenon. During 2010 we did not earn any revenue from our relationship with Xenon.

External Project Funding

CHDI Foundation, Inc.

In August 2011, we renewed our collaboration with CHDI, which we initially entered into in November 2007, to provide us with funding for the discovery and development of an antisense drug for the treatment of Huntington's disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's disease. Under the terms of the new collaboration, we will receive funding from CHDI to identify and conduct IND-enabling studies on an antisense drug targeting the huntingtin gene. If we grant a license to a third party to commercialize our Huntington's disease program, we and CHDI will evenly split the proceeds from the license until CHDI has recouped its funding together with a return determined at a predefined interest rate. Thereafter, we will keep the full amount of any additional proceeds. In addition, CHDI reimbursed us for approximately $1.6 million of research-related expenses we incurred after the earlier collaboration ended in 2010, which we are amortizing over the period of our performance obligation. During 2012, and 2011, we earned revenue of $2.0 million and $2.4 million, respectively, from our relationship with CHDI. In 2010, we did not earn any revenue from our relationship with CHDI. Our balance sheets at December 31, 2012 and 2011 included deferred revenue of $229,000 and $568,000, respectively, related to our relationship with CHDI.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis, or ALS, and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

Technology and Intellectual Property Sale and Licensing Agreements

Out-Licensing Arrangements; Royalty Sharing Agreements; Sales of IP

Abbott Molecular Inc.

In January 2009, we sold our former subsidiary, Ibis Biosciences, to Abbott Molecular Inc., or AMI, pursuant to a stock purchase agreement for a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion.

AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2012, 2011 and 2010 we did not earn any revenue from our relationship with AMI.

Eyetech Pharmaceuticals, Inc. (acquired by Valeant Pharmaceuticals International, Inc.)

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases. Eyetech markets Macugen in the United States and Pfizer Inc. markets the drug outside of the United States. In February 2012, Eyetech was acquired by Valeant Pharmaceuticals International, Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us for the achievement of pre-specified events and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in payments, and our license with Eyetech may also generate additional payments aggregating up to $2.8 million for the achievement of specified regulatory events with respect to the use of Macugen for each additional therapeutic indication. In 2012, 2011 and 2010, we earned $499,000, $790,000 and $567,000, respectively, of revenue related to royalties for Macugen under our license to Eyetech.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. In April 2011, we expanded our relationship with Roche Molecular Systems by granting Roche Molecular Systems a non-exclusive license to additional technology for research and diagnostic uses. During 2012, 2011 and 2010, we earned revenue of $1.0 million, $828,000 and $1.8 million, respectively, from our relationship with Roche Molecular Systems. Our balance sheets at December 31, 2012 and 2011 included deferred revenue of $400,000 and $300,000, respectively, related to our agreements with Roche Molecular Systems.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense its technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of ribonuclease H, or RNase H, patents. During 2012, 2011 and 2010 we earned revenue of $10,000, $10,000 and $20,000, respectively, from our relationship with Idera.

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay milestone payments to the University of Massachusetts totaling up to $500,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive from sublicensing its technology, and a royalty on sales of ISIS-SMN$_{Rx}$ in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to ISIS-FGFR4$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of ISIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $800,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive from sublicensing the Cold Spring Harbor Laboratory's technology, and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

8. Concentration of Business Risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10 percent or more of our total revenue, was as follows:

	2012	2011	2010
Partner A	66%	73%	62%
Partner B	0%	2%	11%
Partner C	8%	18%	9%

Contract receivables from four significant partners comprised approximately 83 percent of our contract receivables at December 31, 2012 and contract receivables from one significant partner comprised approximately 85 percent of our contract receivables at December 31, 2011.

9. Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($17,000 and $22,500 in 2012 for employees under 50 years old and over 50 years old, respectively). We made approximately $529,000, $487,000 and $449,000 in matching contributions for the years ended December 31, 2012, 2011 and 2010, respectively.

10. Legal Proceedings

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1).

On December 28, 2012, a lawsuit was filed against us and certain of our officers on behalf of a class of purchasers of our common stock. The lawsuit sought unspecified monetary damages and generally included allegations that we and certain of our officers violated laws by conditioning investors to believe KYNAMRO would receive US FDA approval for HoFH through materially false and misleading statements regarding KYNAMRO's safety and efficacy. On February 4, 2013, this case was voluntarily withdrawn without prejudice.

11. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2012 and 2011 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2012 Quarters				
Revenue	$ 23,235	$ 47,340	$ 11,601	$ 19,873
Operating expenses	41,690	43,644	39,647	45,992
Income (loss) from operations	(18,455)	3,696	(28,046)	(26,119)
Net loss	$ (23,995)	$ (1,207)	$ (37,639)	$ (2,637)
Basic and diluted net loss per share (1)	$ (0.24)	$ (0.01)	$ (0.37)	$ (0.03)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2011 Quarters				
Revenue	$ 21,147	$ 24,823	$ 20,713	$ 32,403
Operating expenses	37,255	38,883	43,029	51,019
Loss from operations	(16,108)	(14,060)	(22,316)	(18,616)
Net loss	$ (19,994)	$ (17,889)	$ (26,882)	$ (20,036)
Basic and diluted net loss per share (1)	$ (0.20)	$ (0.18)	$ (0.27)	$ (0.20)

(1) We computed net loss per share independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

12. Subsequent Events

In January 2013, we earned a $25 million milestone payment from Genzyme when KYNAMRO was approved for marketing in the United States by the FDA for the treatment of patients with HoFH. In February 2013, we earned a $7.5 million milestone payment from GSK when we initiated the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$.

INDEMNITY AGREEMENT

THIS INDEMNITY AGREEMENT (the "Agreement") is made and entered into this **day of** by and between Isis Pharmaceuticals, Inc., a Delaware corporation (the "Corporation"), and **[name].** ("Agent").

RECITALS

WHEREAS, Agent performs a valuable service to the Corporation in his capacity as **[Title]**;

WHEREAS, the stockholders of the Corporation have adopted bylaws (the "Bylaws") providing for the indemnification of the directors, officers, employees and other agents of the Corporation, including persons serving at the request of the Corporation in such capacities with other corporations or enterprises, as authorized by the Delaware General Corporation Law, as amended ("Delaware Law");

WHEREAS, the Bylaws and Delaware Law by their non-exclusive nature, permit contracts between the Corporation and its agents, officers, employees and other agents with respect to indemnification of such persons; and

WHEREAS, in order to induce Agent to continue to serve as **[Title]**, the Corporation has determined and agreed to enter into this Agreement with Agent;

NOW, THEREFORE, in consideration of Agent's continued service as **[Title],** after the date hereof, the parties hereto agree as follows:

AGREEMENT

1. Services to the Corporation. Agent will serve, at the will of the Corporation or under separate contract, if any such contract exists, as **[Title]** or as a director, officer or other fiduciary of an affiliate of the Corporation (including any employee benefit plan of the Corporation) faithfully and to the best of his ability so long as he is duly elected and qualified in accordance with the provisions of the Bylaws or other applicable charter documents of the Corporation or such affiliate; provided, however, that Agent may at any time and for any reason resign from such position (subject to any contractual obligation that Agent may have assumed apart from this Agreement) and that the Corporation or any affiliate shall have no obligation under this Agreement to continue Agent in any such position.

2. Indemnity of Agent. The Corporation hereby agrees to hold harmless and indemnify Agent to the fullest extent authorized or permitted by the provisions of the Bylaws and Delaware Law, as the same may be amended from time to time (but, only to the extent that such amendment permits the Corporation to provide broader indemnification rights than the Bylaws or Delaware Law permitted prior to adoption of such amendment).

3. Additional Indemnity. In addition to and not in limitation of the indemnification otherwise provided for herein, and subject only to the exclusions set forth in Section 4 hereof, the Corporation hereby further agrees to hold harmless and indemnify Agent:

(a) against any and all expenses (including attorneys' fees), witness fees, damages, judgments, fines and amounts paid in settlement and any other amounts that Agent becomes legally obligated to pay because of any claim or claims made against or by him in connection with any threatened, pending or completed action, suit or proceeding, whether civil, criminal, arbitrational, administrative or investigative (including an action by or in the right of the Corporation) to which Agent is, was or at any time becomes a party, or is threatened to be made a party, by reason of the fact that Agent is, was or at any time becomes a director, officer, employee or other agent of Corporation, or is or was serving or at any time serves at the request of the Corporation as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise; and

(b) otherwise to the fullest extent as may be provided to Agent by the Corporation under the non-exclusivity provisions of Delaware Law and Section 43 of the Bylaws.

4. Limitations on Additional Indemnity. No indemnity pursuant to Section 3 hereof shall be paid by the Corporation:

(a) on account of any claim against Agent for an accounting of profits made from the purchase or sale by Agent of securities of the Corporation pursuant to the provisions of Section 16(b) of the Securities Exchange Act of 1934 and amendments thereto or similar provisions of any federal, state or local statutory law;

(b) on account of Agent's conduct that was knowingly fraudulent or deliberately dishonest or that constituted willful misconduct;

(c) on account of Agent's conduct that constituted a breach of Agent's duty of loyalty to the Corporation or resulted in any personal profit or advantage to which Agent was not legally entitled;

(d) for which payment is actually made to Agent under a valid and collectible insurance policy or under a valid and enforceable indemnity clause, bylaw or agreement, except in respect of any excess beyond payment under such insurance, clause, bylaw or agreement;

(e) if indemnification is not lawful (and, in this respect, both the Corporation and Agent have been advised that the Securities and Exchange Commission believes that indemnification for liabilities arising under the federal securities laws is against public policy and is, therefore, unenforceable and that claims for indemnification should be submitted to appropriate courts for adjudication); or

(f) in connection with any proceeding (or part thereof) initiated by Agent, or any proceeding by Agent against the Corporation or its directors, officers, employees or other agents, unless (i) such indemnification is expressly required to be made by law, (ii) the proceeding was authorized by the Board of Directors of the Corporation, (iii) such indemnification is provided by the Corporation, in its sole discretion, pursuant to the powers vested in the Corporation under Delaware Law, or (iv) the proceeding is initiated pursuant to Section 9 hereof.

5. Continuation of Indemnity. All agreements and obligations of the Corporation contained herein shall continue during the period Agent is a director, officer, employee or other agent of the Corporation (or is or was serving at the request of the Corporation as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise) and shall continue thereafter so long as Agent shall be subject to any possible claim or threatened, pending or completed action, suit or proceeding, whether civil, criminal, arbitrational, administrative or investigative, by reason of the fact that Agent was serving in the capacity referred to herein.

6. Partial Indemnification. Agent shall be entitled under this Agreement to indemnification by the Corporation for a portion of the expenses (including attorneys' fees), witness fees, damages, judgments, fines and amounts paid in settlement and any other amounts that Agent becomes legally obligated to pay in connection with any action, suit or proceeding referred to in Section 3 hereof even if not entitled hereunder to indemnification for the total amount thereof, and the Corporation shall indemnify Agent for the portion thereof to which Agent is entitled.

7. Notification and Defense of Claim. Not later than thirty (30) days after receipt by Agent of notice of the commencement of any action, suit or proceeding, Agent will, if a claim in respect thereof is to be made against the Corporation under this Agreement, notify the Corporation of the commencement thereof; but the omission so to notify the Corporation will not relieve it from any liability which it may have to Agent otherwise than under this Agreement. With respect to any such action, suit or proceeding as to which Agent notifies the Corporation of the commencement thereof:

(a) the Corporation will be entitled to participate therein at its own expense;

(b) except as otherwise provided below, the Corporation may, at its option and jointly with any other indemnifying party similarly notified and electing to assume such defense, assume the defense thereof, with counsel reasonably satisfactory to Agent. After notice from the Corporation to Agent of its election to assume the defense thereof, the Corporation will not be liable to Agent under this Agreement for any legal or other expenses subsequently incurred by Agent in connection with the defense thereof except for reasonable costs of investigation or otherwise as provided below. Agent shall have the right to employ separate counsel in such action, suit or proceeding but the fees and expenses of such counsel incurred after notice from the Corporation of its assumption of the defense thereof shall be at the expense of Agent unless (i) the employment of counsel by Agent has been authorized by the Corporation, (ii) Agent shall have reasonably concluded that there may be a conflict of interest between the Corporation and Agent in the conduct of the defense of such action or (iii) the Corporation shall not in fact have employed counsel to assume the defense of such action, in each of which case the fees and expenses of Agent's separate counsel shall be at the expense of the Corporation. The Corporation shall not be entitled to assume the defense of any action, suit or proceeding brought by or on behalf of the Corporation or as to which Agent shall have made the conclusion provided for in clause (ii) above; and

(c) the Corporation shall not be liable to indemnify Agent under this Agreement for any amounts paid in settlement of any action or claim effected without the Corporation's written consent, which shall not be unreasonably withheld. The Corporation shall be permitted to settle any action except that it shall not settle any action or claim in any manner which would impose any penalty or limitation on Agent without Agent's written consent, which may be given or withheld in Agent's sole discretion.

8. Expenses. The Corporation shall advance, prior to the final disposition of any proceeding, promptly following request therefor, all expenses incurred by Agent in connection with such proceeding upon receipt of an undertaking by or on behalf of Agent to repay said amounts if it shall be determined ultimately that Agent is not entitled to be indemnified under the provisions of this Agreement, the Bylaws, Delaware Law or otherwise.

9. Enforcement. Any right to indemnification or advances granted by this Agreement to Agent shall be enforceable by or on behalf of Agent in any court of competent jurisdiction if (i) the claim for indemnification or advances is denied, in whole or in part, or (ii) no disposition of such claim is made within ninety (90) days of request therefor. Agent, in such enforcement action, if successful in whole or in part, shall also be entitled to be paid the expense of prosecuting his claim. It shall be a defense to any action for which a claim for indemnification is made under Section 7 hereof (other than an action brought to enforce a claim for expenses pursuant to Section 8 hereof, provided that the required undertaking has been tendered to the Corporation) that Agent is not entitled to indemnification because of the limitations set forth in Section 4 hereof. Neither the failure of the Corporation (including its Board of Directors or its stockholders) to have made a determination prior to the commencement of such enforcement action that indemnification of Agent is proper in the circumstances, nor an actual determination by the Corporation (including its Board of Directors or its stockholders) that such indemnification is improper shall be a defense to the action or create a presumption that Agent is not entitled to indemnification under this Agreement or otherwise.

10. Subrogation. In the event of payment under this Agreement, the Corporation shall be subrogated to the extent of such payment to all of the rights of recovery of Agent, who shall execute all documents required and shall do all acts that may be necessary to secure such rights and to enable the Corporation effectively to bring suit to enforce such rights.

11. Non-Exclusivity of Rights. The rights conferred on Agent by this Agreement shall not be exclusive of any other right which Agent may have or hereafter acquire under any statute, provision of the Corporation's Certificate of Incorporation or Bylaws, agreement, vote of stockholders or directors, or otherwise, both as to action in his official capacity and as to action in another capacity while holding office.

12. Survival of Rights.

(a) The rights conferred on Agent by this Agreement shall continue after Agent has ceased to be a director, officer, employee or other agent of the Corporation or to serve at the request of the Corporation as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise and shall inure to the benefit of Agent's heirs, executors and administrators.

(b) The Corporation shall require any successor (whether direct or indirect, by purchase, merger, consolidation or otherwise) to all or substantially all of the business or assets of the Corporation, expressly to assume and agree to perform this Agreement in the same manner and to the same extent that the Corporation would be required to perform if no such succession had taken place.

13. Separability. Each of the provisions of this Agreement is a separate and distinct agreement and independent of the others, so that if any provision hereof shall be held to be invalid for any reason, such invalidity or unenforceability shall not affect the validity or enforceability of the other provisions hereof. Furthermore, if this Agreement shall be invalidated in its entirety on any ground, then the Corporation shall nevertheless indemnify Agent to the fullest extent provided by the Bylaws, Delaware Law or any other applicable law.

14. Governing Law. This Agreement shall be interpreted and enforced in accordance with the laws of the State of Delaware.

15. Amendment and Termination. No amendment, modification, termination or cancellation of this Agreement shall be effective unless in writing signed by both parties hereto.

16. Identical Counterparts. This Agreement may be executed in one or more counterparts, each of which shall for all purposes be deemed to be an original but all of which together shall constitute but one and the same Agreement. Only one such counterpart need be produced to evidence the existence of this Agreement.

17. Headings. The headings of the sections of this Agreement are inserted for convenience only and shall not be deemed to constitute part of this Agreement or to affect the construction hereof.

18. Notices. All notices, requests, demands and other communications hereunder shall be in writing and shall be deemed to have been duly given (i) upon delivery if delivered by hand to the party to whom such communication was directed or (ii) upon the third business day after the date on which such communication was mailed if mailed by certified or registered mail with postage prepaid:

(a) If to Agent, at the address indicated on the signature page hereof.

(b) If to the Corporation, to
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer

or to such other address as may have been furnished to Agent by the Corporation.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement on and as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: _____

Title: _____

AGENT

_____
(signature)

Agent Print Name and Address:

Schedule of Executive Officers and Directors with Indemnity Agreements

Stanley T. Crooke, M.D., Ph.D., Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D., Director, Chief Operating Officer, Secretary, and Director
C. Frank Bennett, Ph.D., Senior Vice President, Antisense Research
Richard S. Geary, Ph.D., Senior Vice President, Development
Elizabeth L. Hougen, Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D., Senior Vice President, Drug Discovery and Corporate Development
Patrick R. O'Neil, Esq., Senior Vice President, Legal and General Counsel
Spencer R. Berthelsen, M.D., Director
Joseph Klein, III, Director
Frederick T. Muto, Esq., Director
Joseph H. Wender, Director

CONFIDENTIAL
EXECUTION COPY

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

AMENDMENT #2 TO RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #2 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment***") is entered into and made effective as of the 30th day of October, 2012 (the "***Amendment Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **GLAXO GROUP LIMITED**, a company existing under the laws of England and Wales, having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England ("***GSK***"). Isis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and GSK are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***");

WHEREAS, Isis and GSK desire to amend the Agreement to more rapidly Develop the drug, ISIS-TTR_{Rx} (ISIS 420915), under the Rare Disease Program focused on the Collaboration Target, Transthyretin (the "***TTR Program***"), which may enable ISIS-TTR_{Rx} to reach registration earlier than originally estimated; and

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, and solely with respect to the TTR Program, the Parties, intending to be legally bound, do hereby agree as follows:

1. TTR Program — Drug Development Activities.

a. **Phase 2 PoC Trial**. The Parties have mutually agreed to a clinical study design for the Phase 2 PoC Trial (as defined hereinafter) for the TTR Program that is reflected in the TTR Development Plan and further described in the other TTR Registration-Directed Program Documents. The Phase 2 PoC Trial for the TTR Program is intended to demonstrate therapeutic benefit in patients with familial amyloid polyneuropathy (FAP). The Phase 2 PoC Trial for the TTR Program and the TTR Registration-Directed Program Documents are intended to support registration filings and Approval of ISIS-TTR_{Rx} on a global basis. The Parties will mutually agree on any material changes to the TTR Registration-Directed Program Documents in accordance with Section 7 of this Amendment.

b. **First Interim Analysis; GSK's Evaluation**. In accordance with the DSMB Charter, the Parties expect the Independent Statistician will perform the First

Interim Analysis and provide the data from such First Interim Analysis (the "***Interim Data Package***") to the DSMB and to each Partner Firewalled Staff. The Parties agree there will be [***] Partner Firewalled Staff members. [***]

c. **Notice of GSK's Decision Whether to Terminate its Option for the TTR Program**.

i. ***GSK Delivers the TTR Termination Notice to Isis.*** GSK will notify Isis within [***] days after the date the Partner Firewalled Staff receive the Interim Data Package if GSK desires to terminate its Option to the TTR Program. If GSK provides written notice to Isis during such [***] period that GSK is terminating its Option to the TTR Program under the Agreement (a "***TTR Termination Notice***"), then (A) GSK will have no further rights or obligations with regard to the TTR Program; (B) GSK's Option to the TTR Program will terminate; and (C) subject to Section 9 of this Amendment and the terms and conditions of the Agreement (as amended by this Amendment), Isis will be free to develop and commercialize any Compounds that were included in the TTR Program on its own or with a Third Party. For clarity, GSK shall have the right under this Section 1.c.i to terminate its Option to the TTR Program irrespective of the outcome of the First Interim Analysis. If Isis notifies GSK within [***] days after Isis' receipt of the TTR Termination Notice that [***]. For clarity, GSK has no obligation to [***].

ii. ***GSK Continues TTR Program***. If GSK does not provide a TTR Termination Notice to Isis during such [***]day period, Isis will continue the Phase 2 PoC Trial for the TTR Program, and GSK will retain its Option to the TTR Program under the Agreement, as modified by this Amendment. Isis will continue enrolling additional patients to complete the Phase 2 PoC Trial in accordance with the TTR Registration-Directed Program Documents and this Amendment.

d. ***Second Interim Analysis (Sample Re-Sizing Analysis) — DSMB Meeting***. If the TTR Program is not terminated pursuant to Section 1c.i. of this Amendment, then, in accordance with the DSMB Charter, the Parties expect the Independent Statistician and the DSMB to perform the Second Interim Analysis and, based on such results the DSMB will notify the Sponsor Primary Contact and the Partner Firewalled Staff members whether or not the DSMB recommends increasing the patient sample size and the number of patients to be added, if any, for the Phase 2 PoC Trial in accordance with the DSMB Charter.

i. ***Adding [***] Patients***. If the DSMB recommends that [***] patients be added to the Phase 2 PoC Trial, then Isis will add such number of patients to the Phase 2 PoC Trial and GSK will fund such additional patients by paying Isis $[***] per such additional patient.

ii. ***Adding [***] Patients.*** If the DSMB recommends that [***] patients (each, a "[***]") be added to the Phase 2 PoC Trial, then, Isis will provide GSK written notice (a ***"[***] Notice"***) of the number of additional patients (if any) Isis intends to add to the Phase 2 PoC Trial within [***] Business days after the DSMB provides such recommendation to the Parties, and either:

1. If the number of additional patients Isis specifies in the [***] Notice is the [***], then Isis will add such number of additional patients to the Phase 2 PoC Trial, and GSK may elect to fund such additional patients at the rate of $[***] per patient by notifying Isis thereof within [***] Business days of GSK's receipt of the [***] Notice.

2. If the number of additional patients Isis specifies in the [***] Notice is (A) [***] or (B) [***], then in either case GSK and Isis will as soon as practicable discuss in good faith the number of additional patients to add to the Phase 2 PoC Trial with the goal of preserving the value of such study. If, within [***] Business Days after the discussion between the Parties, GSK agrees to fund the number of additional patients specified in the [***] Notice, or such number of patients agreed to by the Parties, then Isis will add the number of patients GSK has agreed to fund to the Phase 2 PoC Trial and GSK will fund such additional patients at the rate of $[***] per patient.

If GSK does not agree to fund the additional patients under (y) part 1 of this Section 1.d.ii within [***] Business Days after GSK's receipt of the [***] Notice, or (z) part 2 of this Section 1.d.ii within [***] Business Days after such discussion between the Parties, then Isis will add the number of patients specified in the [***] Notice to the Phase 2 PoC Trial and, GSK will retain its Option to the TTR Program; *provided*, *however*, that [***].

Isis will not add additional patients to the Phase 2 PoC Trial that exceed either (i) the [***] or (ii) [***], whichever is [***], without GSK's written consent.

2. TTR Program — Drug Development Activities and Costs.

a. ***Development Costs Paid by Isis***.

i. ***Before Option Exercise***. Until GSK exercises its Option for the TTR Program, Isis will be responsible for Isis' activities under the TTR Registration-Directed Program Documents and all costs and expenses associated therewith except as otherwise provided under Section 1.d. (Second Interim Analysis (Sample Re-Sizing Analysis) — DSMB Meeting), Section 2.b. (Development Costs Paid by GSK), Section 3. (Supply Chain Strategy) or Section 4.d. (Compensation for Activities Performed by Isis) of this Amendment.

ii. ***Contract Clinical Trial Services by GSK in [***] and/or [***]***. If the Parties mutually agree to include patients in [***] and/or [***] in the Phase 2 PoC Trial, Isis will engage GSK or GSK's Affiliates in [***] and/or [***] (as applicable) to provide contract clinical study services under a clinical study services agreement with customary terms and conditions, including, without limitation, [***]. In exchange, Isis will pay GSK or GSK's Affiliate a fee for such services at a rate of $[***] per enrolled patient that completes i) the [***] or ii) the [***], as defined in the Protocol, and Isis will make such payment within sixty (60) days after Isis' receipt of an invoice from GSK or GSK's Affiliate.

iii. ***[***] Services by GSK***. If the Parties mutually agree to engage GSK or GSK's Affiliates to perform [***] services for the Phase 2 PoC Trial, Isis will engage GSK or GSK's Affiliates to perform [***] services for the Phase 2 PoC Trial, with any mutually agreed fees (but in no event will such fees be [***]), and Isis will make such payment within sixty (60) after Isis' receipt of an invoice from GSK or GSK's Affiliate.

b. ***Development Costs Paid by GSK***.

i. ***Before Option Exercise.***

1. ***Additional Costs***. GSK will be responsible for paying the Additional Costs resulting from Approved Changes in the manner as agreed to by the Parties pursuant to Section 7.b. On a quarterly basis, Isis will deliver to GSK an invoice for such portion of the Additional Costs that are allocated for the activities for the coming quarter [***], which GSK will pay each such invoice within [***] days after GSK's receipt.

2. ***Costs Associated with Additional Patients***. With respect to the additional patients that GSK is obligated to fund pursuant to Section 1.d.i or agrees to fund pursuant to Section 1.d.ii.1 or Section 1.d.ii.2, GSK will fund each such additional patient at

$[***] per patient, and will remit payment of such amount to Isis as follows:

i. $[***] for each such additional patient [***] within [***] days after GSK's receipt of an invoice from Isis; and

ii. When at least [***] of such additional patients are enrolled in the Phase 2 PoC Trial, the remaining $[***] for each such additional patient [***] within [***] days after GSK's receipt of an invoice from Isis.

ii. ***After Option Exercise***.

1. ***Generally***. Without limiting the Agreement, after GSK exercises the Option for the TTR Program, GSK will be solely responsible for and have sole decision making authority over all Development and Commercialization activities, and will be solely responsible for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Licensed Compounds and related Licensed Products, including, but not limited to, the costs and expenses of completing any uncompleted activities under the TTR Registration-Directed Program Documents, but excluding [***].

2. ***Technology Transfer; Transition Services***. Without limiting the Agreement, after GSK exercises the Option for the TTR Program, Isis will transfer all Licensed Know-how (including all regulatory approvals and regulatory materials and clinical and non-clinical studies relating to the TTR Program) to GSK and provide transition services to GSK in accordance with Section 4.2.1 of the Agreement and additional services upon GSK's request in accordance with Section 4.2.2 of the Agreement. The Parties acknowledge that, due to the nature of this Amendment, certain transition services of the transition services provided in accordance with Section 4.2.1 or 4.2.2 of the Agreement may need to be initiated prior to Option exercise, and Isis agrees to use its Commercially Reasonable Efforts to assist with such transition services as requested by GSK, taking into consideration the need for an efficient transition to continue successful Development and Commercialization of ISIS-TTR$_{Rx}$.

3. ***Transfer of the Sponsorship of the OLE Study***. Without limiting the Agreement, after GSK exercises the Option for the TTR Program, Isis will transfer the sponsorship of the OLE Study to GSK and at GSK's option and expense, all of the responsibilities thereunder to GSK. If GSK opts not to have the responsibilities thereunder transferred from Isis to GSK, GSK shall promptly enter

into a services agreement, pursuant to which GSK will engage Isis at GSK's expense to continue its activities to oversee and manage the OLE Study on terms and conditions agreed to by both Parties.

3. Supply Chain Strategy.

a. Mutually Agreed Strategy. Subject to this Section 3.a of this Amendment, Isis will be responsible for manufacturing (or having manufactured) a sufficient quantity of API and finished product to complete the Phase 2 PoC Trial and the Phase 2 PoC Trial Support Activities. By the [***] following the Amendment Date, the Parties will form a CMC sub-team (the "***CMC Sub-Team***") pursuant to Section 6.a, which will discuss and, by [***] agree upon, a high level supply chain strategy to supply API and finished product for Commercialization of Licensed Products ("***Commercial Supplies***"), and GSK will have the final decision-making authority regarding the strategy and steps towards development of Commercial Supplies as well as clinical supplies after GSK's exercise of the Option.

b. Isis May Supply API for Initial Commercialization.

i. ***Isis May Supply API to GSK for Initial Commercialization***. In support of obtaining Approval and Commercialization of Licensed Products, the Parties may by separate agreement mutually agree that GSK will contract with Isis for Isis to manufacture and supply API for commercial launch of Licensed Products and for a post-launch Commercialization period of up to [***] (unless the Parties otherwise agree to a longer period), pursuant to a commercial supply agreement (the "***Isis-GSK Commercial API Supply Agreement***"). In addition, GSK and Isis may enter into a mutually agreed services agreement (the "***Services Agreement***") pursuant to which Isis will perform validation work, manufacture and supply validation lots (if not included under the Isis API Commercial Supply Agreement) and registration stability lots to GSK and prepare the draft of the chemistry, manufacturing and controls ("***CMC***") section for the NDA, MAA or other marketing authorization applications.

ii. ***API Manufacturing Technology Transfer***. The Isis-GSK Commercial API Supply Agreement will provide that, no later than [***] prior to the [***], Isis will, in accordance with and subject to the general technology transfer principles described in Section 4.2.1 of the Agreement, in accordance with [***] conduct a technology transfer to GSK (or GSK's designated Third Party supplier) of all technology, information and data related to Isis' manufacturing and supply of the API, and Isis will continue to supply API to GSK for [***] to enable GSK to (i) identify and contract with a suitable Third Party API manufacturer or (ii) transfer the manufacture of API to a qualified GSK manufacturing site. Such API manufacturing technology transfer will be initiated earlier if GSK desires

to establish a back-up manufacturing facility or if Isis fails to supply API as required under the Isis-GSK Commercial API Supply Agreement.

c. Manufacturing of Finished Product by GSK.

i. ***GSK to Manufacture Finished Product***. Subject to the terms of this Section 3.c.i and the terms of the Agreement (as amended by this Amendment), GSK will manufacture and supply finished product and corresponding placebo (new supply) for the Phase 2 PoC Trial and/or the Phase 2 PoC Trial Support Activities. In addition, the Parties acknowledge that, subject to the terms of this Section 3.c.i and the terms of the Agreement (as amended by this Amendment), GSK will manufacture or have manufactured finished product for Commercialization.

ii. ***GSK-Isis Finished Product Supply Agreement for Clinical Studies***. The terms for any such transfer and supply of finished product and corresponding placebo (new supply) by GSK for the Phase 2 PoC Trial and/or the Phase 2 PoC Trial Support

Activities will be pursuant to mutually agreed supply and quality agreement(s) (the "***GSK-Isis Finished Product Supply Agreement for Clinical Studies***"), with GSK to be compensated for its manufacture of any finished product (or placebo) used in the Phase 2 PoC Trial in an amount equal to $[***] per finished product/placebo batch fill (with the batch size to be mutually agreed). The GSK-Isis Finished Product Supply Agreement for Clinical Studies will include the manufacturing technology transfer provisions set forth in Section 3ciii below, and will also contain, but not be limited to, the terms only for supply of finished product (or placebo) for the Phase 2 PoC Trial and Phase 2 PoC Trial Support Activities. The prices for GSK to supply finished product (or placebo) other than for the Phase 2 PoC Trial and Phase 2 PoC Trial Support Activities will be [***].

iii. ***Finished Product Manufacturing Technology Transfer***.

1. ***Initial Finished Product Manufacturing Technology Transfer from Isis to GSK***. To facilitate GSK in manufacturing the finished product for the Phase 2 PoC Trial, the Phase 2 PoC Trial Support Activities, and Commercialization, the Parties will collaborate to facilitate a technology transfer to a finished product manufacturing site identified by GSK in support thereof. Isis will be compensated by GSK for Isis' technology transfer efforts based on a mutually agreed plan, including, the cost of Isis' time incurred in performing such work at [***] plus any reasonable out-of-pocket expenses incurred by Isis in performing such work. Isis will invoice GSK for any such work and costs and GSK will pay the invoices submitted within [***] days after receipt of the applicable invoice by GSK.

2. ***Manufacturing Technology Transfer from GSK to Isis at Termination***. If the Agreement terminates or the Option for the TTR Program is terminated or expires unexercised, Isis may request GSK to conduct a technology transfer to Isis (or Isis' designated Third Party supplier) of any technology, information and data reasonably related to GSK's manufacturing and supply of such finished product, and if so requested, GSK will, [***], conduct such a technology transfer and GSK will continue to (i) provide reasonable support and cooperation with Isis' regulatory filings and interactions with Regulatory Authorities related to GSK's finished product manufacturing (including any required inspections), and (ii) supply finished product to Isis, [***] to enable Isis to identify and contract with a suitable Third Party finished product manufacturer. Notwithstanding, any termination or expiration of the Option, Isis agrees to include GSK among the third party contract manufactures being evaluated for the manufacture and supply of finished product, whether for clinical trials or Commercialization.

4. **Collaboration in Regulatory Activities**.

a. ***Regulatory Plan***. Isis and GSK will form a regulatory subteam (the "***Regulatory Sub-Team***") pursuant to Section 6.a, which will produce a high-level outline, [***], which outline to be mutually agreed no later than [***]. Following the First Interim Analysis, the Regulatory Sub-Team, in collaboration with other sub-teams formed hereunder, will mutually develop and agree to a detailed plan for coordination and preparation of the NDA and MAA for ISIS-TTR$_{Rx}$ (including establishing responsibilities for provision of all sections of the electronic common technical document ("***eCTD***") modules, authorship, plan activity timelines and any associated costs and expenses, including any work GSK would like Isis to perform) to ensure a smooth transition to GSK, accelerate eCTD completion and facilitate rapid NDA, MAA and JNDA filings. Once the Parties mutually agree upon such a plan, each Party will use Commercially Reasonable Efforts to execute their respective tasks and responsibilities under such plan in the time frames set forth in such plan.

b. ***GSK's Participation in Regulatory Activities***. With respect to the TTR Program, prior to Option exercise, Isis will keep GSK informed about its regulatory activities and communications it has with the Regulatory Authorities. Isis will provide as much advance notice as possible to GSK and [***] after its receipt of the notice from a Regulatory Authority about its meetings or conference calls it will have with such Regulatory Authority, and provide GSK with a reasonable opportunity to participate as an observer in the meeting at GSK's expense to provide Isis with information and suggestions. In addition, Isis will provide GSK with full access to all available documentation needed by GSK in preparing NDA, MAA and other marketing authorization applications, in addition to other

regulatory activities as well as GSK's preparation for interacting with Regulatory Authorities.

c. ***Isis' Participation in Regulatory Activities***. After Option exercise, GSK will provide advance notice to Isis promptly after its receipt of a notice from a Regulatory Authority about any meetings or conference calls GSK will have with such Regulatory Authority and, at GSK's discretion, will provide Isis with a reasonable opportunity to participate as an observer in the meeting at Isis' expense to provide GSK with information and suggestions. GSK will inform Isis about its regulatory activities in a summary format and material communications it has with the Regulatory Authorities that may affect the TTR Program or other Collaboration Programs.

d. ***Compensation for Activities Performed by Isis***. In accordance with Section 4.2.2 of the Agreement, GSK will pay Isis for Isis' time in performing Isis' regulatory plan activities described in Section 4.a of this Amendment at [***]. GSK may request assistance from Isis prior to Option exercise, and Isis will consider any such request in good faith.

5. **Option**. Following GSK's receipt of the PoC Trial Completion Notice (including the Phase 2 PoC Data Package as defined in this Amendment) for the TTR Program, GSK will provide written notice to Isis of its decision whether or not to exercise its Option to the TTR Program under Section 3.1 of the Agreement as soon as possible, but in any case, on or before 5:00 p.m. (Eastern time) on the [***] ([***]) day following GSK's receipt of the PoC Trial Completion Notice (the "***Option Deadline***"). If GSK does not provide written notice to Isis of GSK's determination to license the TTR Program before the Option Deadline, then GSK's Option to the TTR Program will expire and, subject to Section 9 of this Amendment and the terms of the Agreement (as amended by this Amendment), Isis will be free to Develop and Commercialize any Compounds that were included in the TTR Program on its own or with a Third Party.

6. TTR Steering Committee.

a. ***Formation of the TTR Steering Committee***. Within [***] after the Amendment Date, with respect to the TTR Program, the Parties will establish a TTR steering committee ("***TTR Steering Committee***") that will be separate and independent from the JSC, and which will be responsible for the coordination and management of activities to develop the regulatory strategy and CMC strategy through Option exercise to enable a smooth transition of such activities. The TTR Steering Committee will consist of three representatives of Isis and three representatives of GSK. The TTR Steering Committee may elect to create sub-teams designated to address the following areas: (i) regulatory; (ii) CMC; and (iii) clinical, with representatives responsible for ensuring that activities occur as set forth in this Amendment and the TTR Registration-Directed Program Documents. The TTR Steering Committee will operate in accordance with the same operating procedures for the JSC as set forth in Section 1.3.1 of the Agreement.

b. ***Roles of the TTR Steering Committee and Sub-Teams Formed Thereunder***. Subject to Section 6.c of this Amendment and solely in connection with the TTR Program, the TTR Steering Committee (or any sub-teams formed by the TTR Steering Committee) will perform the following functions, some or all of which may be addressed directly at any given meeting of the TTR Steering Committee or a sub-team:

i. review the TTR Registration-Directed Program Documents from time to time and prepare Material Amendments, if any, to the TTR Registration-Directed Program Documents;

ii. develop CMC strategy and manage development activities, including process development, formulation development, quality control, stability tests, scale up, etc.;

iii. manage the manufacture and supply of API and/or finished product for Clinical Studies;

iv. review and oversee the clinical monitoring program and the statistical analysis plan (including establishing a mutually agreed process for GSK to participate in in-stream safety data review with Isis);

v. develop regulatory strategy and coordinate, review and oversee regulatory activities conducted under the TTR Registration-Directed Program Documents;

vi. facilitate sharing of data and information between the Parties' regulatory teams to ensure each Party's access to all data;

vii. coordinate meetings and other interactions (including written correspondence) with Regulatory Authorities;

viii. develop a transition plan prior to GSK's exercise of the Option, including coordinating the transfer of manufacturing technology and delivery of regulatory materials, and execute such plan; and

ix. such other review and advisory responsibilities as may be assigned to the TTR Steering Committee pursuant to this Amendment or as may be mutually agreed upon in writing by the Parties from time to time.

c. ***Decision Making***. The Parties will conduct the TTR Program in accordance with the TTR Registration-Directed Program Documents, giving due consideration to the recommendations and advice of the TTR Steering Committee. Isis will have the final decision-making authority regarding [***].

d. ***Briefing the TTR Steering Committee*****.** At each regularly scheduled meeting of the TTR Steering Committee, Isis will provide to the TTR Steering Committee [***].

e. ***Term of TTR Steering Committee***. The TTR Steering Committee (and any of its sub-teams and working groups) under this Amendment will cease to exist upon the earlier of exercise, termination or expiration of the Option with respect to the TTR Program.

f. ***Meeting Coordination***. The TTR Steering Committee will meet at least once per quarter in person or via video teleconference or conference and more frequently whenever necessary and will meet in person at least twice a year. Isis and GSK will use commercially reasonable efforts to schedule meetings of the JSC and TTR Steering Committee to take place at the same location and on the same dates to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

7. Material Amendments to the TTR Registration-Directed Program Documents.

a. ***Overview***. As of the Amendment Date, the Parties have agreed to the TTR Development Plan (which is attached hereto as ATTACHMENT 1), as well as the SPA, the Protocol and the DSMB Charter, all of which have been delivered to each Party under separate cover.

b. ***Material Amendment Process***. No material amendment to any TTR Registration-Directed Program Document (each, a "***Material Amendment***") may be made without both Parties' prior written consent. If any Regulatory Authority requires or, based on feedback from a Regulatory Authority, either Party requests a change to the Phase 2 PoC Trial or any TTR Registration-Directed Program Document that requires the Parties to make a Material Amendment to a TTR Registration-Directed Program Document to affect such a change, the Parties will use good faith and commercially reasonable efforts to mutually agree on such a Material Amendment (including any associated Additional Costs and the payment schedule thereof) to such TTR Registration-Directed Program Document within [***] days of receiving such proposed change from such Regulatory Authority or a Party. If

the Parties mutually agree to such a Material Amendment (including any associated Additional Costs and the payment schedule thereof), Isis will continue to perform the Phase 2 PoC Trial in accordance with such amended TTR Registration-Directed Program Documents. If, despite the Parties' good faith and commercially reasonable efforts, the Parties cannot agree (i) on such a Material Amendment to such TTR Registration-Directed Program Document (including any associated Additional Costs and the payment schedule thereof) or (ii) whether such an amendment is a Material Amendment, in each case, within [***] days of receiving such proposed change from such Regulatory Authority or a Party, the dispute will be promptly (but no later than [***] days after the end of such [***] day period) referred to the [***]. If the [***] cannot resolve the matter within [***] Business Days after receiving such dispute then:

i. if the dispute arose [***], then [***]; or

ii. if the dispute arose [***], then [***].

c. ***Non-Material Amendments***. Isis will consider in good faith any changes to any TTR Registration-Directed Program Documents that are requested by GSK that do not require the Parties to make a Material Amendment to a TTR Registration-Directed Program Document to affect such a change.

8. **Financial Provisions**. The following financial provisions will apply solely to the TTR Program:

a. ***Upfront Fee***. GSK will pay Isis $2,500,000 within [***] days of GSK's receipt of the invoice from Isis following the Amendment Date.

b. ***Milestone Payments for First Achievement of Development Milestone Event***. Solely with respect to a Compound under the TTR Program that first achieves a Development Milestone Event by or on behalf of GSK or its Affiliates or Sublicensees, Table 2 set forth in Section 5.5.1 (Milestone Payments for First Achievement of Development Milestone Event) of the Agreement is deleted in its entirety and replaced with TABLE X below:

TABLE X

Development Milestone Events for a Compound		Milestone Payment
Initiation of the Phase 2 PoC Trial	$	7,500,000
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
[***]	$	[***]
Total Development Milestone Payments for the TTR Program	**$**	**[***]**

"***Dosing***" or "***Dosed***" means, with respect to the above milestone events, administration of the first dose of ISIS-TTR_{Rx} or placebo to the applicable patient in the Phase 2 PoC Trial in accordance with the TTR Registration-Directed Program Documents.

Notwithstanding Section 5.8.2 of the Agreement, Isis will send GSK a written notice promptly following the date when the "*Initiation of the Phase 2 PoC Trial*" Milestone Event in TABLE X is achieved, and the $7,500,000 milestone payment will be due within [***] Business Days of GSK's receipt of the invoice.

c. ***TTR Program Option Exercise Fee***. Upon the exercise by GSK of the Option for the TTR Program in accordance with the Agreement (as amended by this Amendment), in lieu of the Option exercise fee set forth in Column 1 of Table 1 in Section 5.4 (Option Exercise Fees) of the Agreement, GSK will pay Isis an Option exercise fee of $[***] ([***]), within [***] days after receipt by GSK of an invoice sent from Isis on or after such Option exercise becomes effective under the Agreement (as amended by this Amendment).

d. ***Milestone Payments for First Achievement of Sales Milestone Event***. Solely with respect to a Licensed Product under the TTR Program, TABLE 4 set forth in

Section 5.7.1 (Milestone Payments for First Achievement of Sales Milestone Event) of the Agreement is deleted in its entirety and replaced with TABLE Y below:

TABLE Y

Sales Milestones for Licensed Products in the TTR Program	Milestone Payment
$[***] in worldwide Annual Net Sales	$ [***]
$[***] in worldwide Annual Net Sales	$ [***]
$[***] in worldwide Annual Net Sales	$ [***]
$[***] in worldwide Annual Net Sales	$ [***]
$[***] in worldwide Annual Net Sales	$ [***]
Total Sales Milestone Payments for the TTR Program	**$ [***]**

9. **TTR Program Reverse Royalties**. Solely with respect to any Discontinued Products for which GSK has [***], TABLE 6 set forth in Section 5.10.1 (Reverse Royalty for Discontinued Products) of the Agreement is deleted in its entirety and replaced with TABLE Z below:

TABLE Z

Development/Regulatory Status of Discontinued Product at time of reversion under this Agreement	Applicable Royalty Rate on worldwide Annual Net Sales of Discontinued Product
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%

10. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment, the Agreement remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment is solely intended to modify certain

terms of the Agreement regarding the TTR Program, and does not amend the Agreement in any way with respect to the other Collaboration Programs.

11. **Termination for a Safety Concern**.

a. ***Required by Regulatory Authorities or Mutually Agreed***. If a Safety Concern arises that causes (i) the DSMB or any Regulatory Authority to require that the Phase 2 PoC Trial be placed on clinical hold or terminated or (ii) the Parties to agree that the Phase 2 PoC Trial should be terminated, then in each case termination of the Phase 2 PoC Trial should be initiated within [***] ([***]) days after such request or agreement and GSK may terminate its Option to the TTR Program with thirty (30) days advance notice.

b. ***Not Required by Regulatory Authorities or Mutually Agreed.*** If a Safety Concern arises that causes the DSMB, any Regulatory Authority, or GSK's Global Safety Board to recommend (but not require) that the Phase 2 PoC Trial be placed on clinical hold or terminated and the Parties cannot agree on whether the Phase 2 PoC Trial should be placed on clinical hold or terminated, the Parties will promptly (but no later than fifteen (15) days after such Safety Concern arises) meet and confer to discuss such Safety Concern and use good faith efforts to resolve such Safety Concern in a manner that permits continuation of the Phase 2 PoC Trial. If, after such good faith discussions (including discussions with the DSMB), such Safety Concern cannot be resolved to GSK's satisfaction, GSK will have the right to terminate its Option to the TTR Program by providing Isis written notice, which termination will become effective on the thirtieth (30^{th}) day following Isis' receipt of such termination notice.

c. ***Consequences of Termination***. If GSK terminates its Option to the TTR Program under Section 11.a or Section 11.b of this Amendment, (i) GSK will have no obligation to [***], (ii) Isis will have no obligation to [***] and (iii) GSK will [***] if Isis directs, by written notice, the clinical research organization that is engaged to conduct the Phase 2 PoC Trial to begin the process of terminating the Phase 2 PoC Trial within thirty (30) days after GSK's termination notice.

12. **Restriction on GSK's Right to Terminate for Convenience**. Except in accordance with Section 1.c.i, Section 11.a or Section 11.b of this Amendment, or Section 9.2.2, Section 9.2.3(a) or Section 9.2.5 of the Agreement, GSK will not have the right to terminate the Agreement with respect to the TTR Program (or terminate this Amendment) until GSK's Option to the TTR Program expires.

13. **Definitions**. Capitalized terms not otherwise defined herein will have the meanings given in the Agreement. For purposes of this Amendment, the following capitalized terms will have the following meanings:

a. "[*******]" has the meaning set forth in Section 1.d of this Amendment.

b. "***Additional Costs***" means, [***].

c. "***Approved Changes***" means any changes (including duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the TTR Registration-Directed Program Documents (including any Material Amendments) that are requested by GSK or required by a Regulatory Authority and mutually agreed by GSK and Isis.

d. "***CMC***" has the meaning set forth in Section 3.b.i of this Amendment.

e. "***CMC Sub-Team***" has the meaning set forth in Section 3.a of this Amendment.

f. "***Commercial Supplies***" has the meaning set forth in Section 3.a of this Amendment.

g. "***Dosing***" has the meaning set forth in Section 8.b of this Amendment.

h. "***DSMB***" means the Data and Safety Monitoring Board for the Phase 2 PoC Trial for the TTR Program.

i. "***DSMB Charter***" means the charter that governs the activities and duties of the DSMB and its members which was submitted to the FDA on [***], as may be amended from time to time pursuant to Section 7 of this Amendment.

j. "***eCTD***" has the meaning set forth in Section 4.a of this Amendment.

k. "***First Interim Analysis***" means the first interim analysis described in the DSMB Charter.

l. "***GSK-Isis Finished Product Supply Agreement for Clinical Studies***" has the meaning set forth in Section 3.c.ii of this Amendment.

m. "***Independent Statistician***" has the meaning ascribed to it in the DSMB Charter.

n. "***Initiation of the OLE Study***" means the date the first human patient enrolled in the Phase 2 PoC Trial for the TTR Program reaches the [***] time point in such Phase 2 PoC Trial.

o. "***Initiation of the Phase 2 PoC Trial***" means [***].

p. "***Interim Data Package***" has the meaning set forth in Section 1.b of this Amendment.

q. "***ISIS-TTR$_{Rx}$***" means the Compound known as ISIS 420915.

r. "***Isis-GSK Commercial API Supply Agreement***" has the meaning set forth in Section 3.b.i of this Amendment.

s. "***Material Amendment***" has the meaning set forth in Section 7.b of this Amendment.

t. "***OLE Study***" means the open label extension study of ISIS-TTR$_{Rx}$ described in the TTR Development Plan.

u. "***Option Deadline***" has the meaning set forth in Section 5 of this Amendment.

v. "***Partner Firewalled Staff***" has the meaning set forth in the DSMB Charter.

w. "***Phase 2 PoC Data Package***" means, with respect to ISIS-TTR$_{Rx}$, (i) [***], (ii) [***], (iii) [***], (iv) [***], (v) copies of all filings submitted to Regulatory Authorities regarding ISIS-TTR$_{Rx}$, (vi) [***], and (vii) [***] together with the foregoing information listed in clause (i) through (vi), to the extent available, with respect to the [***] of ISIS-TTR$_{Rx}$.

x. "***Phase 2 PoC Trial***" means, with respect to ISIS-TTR$_{Rx}$, the Phase 2/3, multicenter, double-blind, randomized, stratified, placebo-controlled study of ISIS-TTR$_{Rx}$ in Stage 1 and Stage 2 FAP patients with [***], as described in the TTR Registration-Directed Program Documents that is intended to be used for the global registration of ISIS-TTR$_{Rx}$.

y. "***Phase 2 PoC Trial Support Activities***" means the [***] and the [***] identified under the "*Phase 2 PoC Trial Support Activities*" section of the TTR Development Plan.

z. "***Protocol***" means the protocol No. ISIS 420915-CS2 entitled "A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy" for the conduct of the Phase 2 PoC Trial which was submitted to the FDA on [***], as may be amended from time to time pursuant to Section 7 of this Amendment.

aa. "***Regulatory Sub-Team***" has the meaning set forth in Section 4.a of this Amendment.

bb. "***Reviewing Entity***" means an institutional review board (IRB), research ethics board (REB), European ethical committee (EEC), or equivalent appropriate governmental ethical reviewing entity responsible for approving an entity to participate in the Phase 2 PoC Trial as a clinical site.

cc. "***Safety Concern***" means [***].

dd. "***Second Interim Analysis***" means the second interim analysis described in the DSMB Charter.

ee. "***Services Agreement***" has the meaning set forth in Section 3.b.i of this Amendment.

ff. "***SPA***" or "***Special Protocol Assessment***" means the request for special protocol assessment for the Phase 2 PoC Trial which was submitted by Isis to FDA.

gg. ***"Sponsor Primary Contact"*** has the meaning set forth in the DSMB Charter.

hh. "***TTR Development Plan***" means the Development plan attached to this Amendment as ATTACHMENT 1, as may be amended from time to time pursuant to Section 7 of this Amendment.

ii. "***TTR Registration-Directed Program Documents***" means the TTR Development Plan, the SPA, the Protocol and the DSMB Charter.

jj. "***TTR Steering Committee***" has the meaning set forth in Section 6.a of this Amendment.

kk. "***TTR Termination Notice***" has the meaning set forth in Section 1.c.i of this Amendment.

* - * - * - *

[Signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives as of the Amendment Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer and Chief Financial Officer

Date: 29 October 2012

GLAXO GROUP LIMITED

By: */s/ Paul Williamson*

Name: Paul Williamson

Title: Corporate Director

Date: 29 October 2012

ATTACHMENT 1

TTR Development Plan

[***]

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

ASTRAZENECA AB

COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

This COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT (the "***Agreement***") is entered into as of the 7th day of December, 2012 (the "***Effective Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **ASTRAZENECA AB**, a company incorporated in Sweden under no. 556011-7482 with offices at SE-151 85 Södertälje, Sweden ("***AstraZeneca***"). AstraZeneca and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis has expertise in discovering and developing antisense drugs for cancer and is (i) developing ISIS-STAT3$_{Rx}$ in a Phase 1/2 Trial in patients with cancer, (ii) working to identify an antisense oligonucleotide targeting the gene target, [***] for the treatment of cancer, and (iii) conducting drug discovery efforts for numerous other cancer targets;

WHEREAS, AstraZeneca has expertise in developing and commercializing human therapeutics, and is interested in developing and commercializing ISIS-STAT3$_{Rx}$, and drugs targeting [***] and other cancer targets; and

WHEREAS, AstraZeneca desires Isis to (i) grant AstraZeneca an exclusive license to Isis' STAT3 Program and [***] Program, (ii) conduct research and development activities for the STAT3 Program and [***] Program, and (iii) collaborate with Isis to identify a development candidate for each of three separate cancer-related genes, and with respect to drugs targeting such genes, to grant an option to exclusively license the programs associated with such genes;

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
STAT3 DEVELOPMENT PROGRAM

1.1. **STAT3 Program Overview**. The intent of the STAT3 Program is (i) for Isis to complete the ongoing Phase 1/2 Trial for ISIS-STAT3$_{Rx}$; and (ii) for AstraZeneca to perform all other preclinical, clinical (including conducting the [***]), regulatory and commercial activities related to STAT3 Products. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to ISIS-STAT3$_{Rx}$, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **STAT3 Research and Development Responsibilities**.

1.2.1. **STAT3 Research and Development Plan Activities; Timelines**. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under the STAT3 Research and Development Plan in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under the STAT3 Research and Development Plan in accordance with the timelines specified therein.

1.2.2. **STAT3 Research and Development Plan**. The Parties will continue to develop and refine the STAT3 Research and Development Plan initially agreed at the Effective Date as needed and update it at least once each six months, and submit it to the JSC for its review and comment. Subject to Section 4.1.4, any material changes to the STAT3 Research and Development Plan must be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. On a rolling basis, the STAT3 Research and Development Plan will contain activities for at least the next [***], including the key Development and regulatory decisions for ISIS-STAT3$_{Rx}$ and the key factors that will be considered when making such Development and regulatory decisions.

1.2.3. **Phase 1/2 Trial**.

(a) **High Response Outcome Analysis**. A "***High Response Outcome***" is achieved when the [***].

(b) **Medium Response Outcome Analysis**. A "***Medium Response Outcome***" is achieved if, [***]. If there has not been a [***] in at least [***] of the evaluable DLBCL Patients in the Phase 1/2 Trial, then there has been a "***Low Response Outcome.***"

For purposes of this Agreement, "***Durable Response***" means [***]. DLBCL Patients who achieve a Durable Response at [***] of treatment with ISIS-STAT3$_{Rx}$ but who are discontinued from the Phase 1/2 Trial before 24 weeks of treatment due to electing to receive a bone marrow transplant (a "***BMT Patient***") will be [***]; *provided, however*, that no more than [***] BMT Patients will be [***] for purposes of determining whether a High Response Outcome has been achieved and no more than [***] BMT Patient will be [***] for purposes of determining whether a Medium Response Outcome has been achieved.

(c) **Target Knock-Down**. "***Target Knock-Down***" means [***]. The [***] sample must contain [***]. The [***] sample will be taken within [***]. Analysis can be based on results from [***]. The JSC will unanimously decide on [***]. The selected pathology laboratory that conducts Target Knockdown analysis will report the results of this analysis to the JSC which will review whether the Target Knockdown criteria have

been achieved. The success criteria for Target Knock-Down requires [***]. The JSC will review the [***] on an ongoing basis with respect to quality of samples, post-treatment sampling time point, and technical challenges associated with measuring the [***]. If the JSC unanimously agree to a change in the Target Knock-Down criteria based on this ongoing data review, the criteria to meet the Target Knock-Down component of the response outcome will be amended. If there is a High Response Outcome and at least [***], then Target Knock-Down will [***].

(d) **Safety Concern**. For purposes of this Agreement, "***Safety Concern***" means [***].

(e) **Notice of High Response Outcome, Medium Response Outcome or Low Response Outcome**. Promptly following Isis' determination that a High Response Outcome, Medium Response Outcome or Low Response Outcome has occurred, Isis will provide AstraZeneca with written notice (an "***Outcome Notice***") of whether (i) there is a High Response Outcome (and whether at least [***]), Medium Response Outcome or Low Response Outcome, (ii) there is a Safety Concern, and (iii) Target Knock-Down was achieved, and will include with such Outcome Notice the available components of the Phase 1/2 Trial Data Package. AstraZeneca may dispute Isis' determination regarding any of items (i), (ii) or (iii) described in this Section 1.2.3(e), by providing Isis written notice thereof within 30 days of AstraZeneca's receipt of the Outcome Notice (in which case Section 1.2.4 will apply); otherwise the determinations set forth in the Outcome Notice will be binding on the Parties.

(f) **AstraZeneca's Response to the Phase 1/2 Trial Data Package**.

(i) If either (a) Target Knock-Down was not achieved and there was [***]; or (b) there is a Low Response Outcome; or (c) there is a Safety Concern (in each case whether determined under Section 1.2.3(e) or the Third Party expert under Section 1.2.4), then within 10 Business Days of the Outcome Notice or determination of the Third Party expert under Section 1.2.4 (as applicable) if AstraZeneca either (x) provides Isis with a written notice that it wishes to terminate the license granted by Isis to AstraZeneca under Section 6.1.1, or (y) does not provide any written notice as to whether or not it wishes to terminate the license or continue with the license, the license granted by Isis to AstraZeneca under Section 6.1.1 will terminate and no milestone payment for ISIS-STAT3$_{Rx}$ will be payable.

(ii) If either (a) AstraZeneca provides Isis with a written notice that it wishes to continue with the license under Section 6.1.1

despite its option to terminate its license to STAT3 Products under Section 1.2.3(f)(i) within the timeline specified therein, or (b) if such Section 1.2.3(f)(i) does not apply, then in the case of a High Response Outcome, Medium Response Outcome or Low Response Outcome (in each case whether determined under Section 1.2.3(e) or the Third Party expert under Section 1.2.4), the applicable milestone payment under TABLE 1 in Section 8.4 will become due following such determination, and AstraZeneca will pay Isis such milestone payment within 30 days after receipt of an invoice from Isis. In addition, if there is a Medium Response Outcome, at the next meeting of the JSC, AstraZeneca will indicate whether it plans to [***].

(g) **AstraZeneca's Continued Development Following Phase 1/2 Trial Data Package**. Without limiting Section 1.2.1 or Section 7.1:

(i) If the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) and there is a High Response Outcome (or there is a Medium Response Outcome *but* AstraZeneca plans to [***]), then *provided* Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(i), AstraZeneca will initiate a clinical study for ISIS-STAT3$_{Rx}$ in accordance with the STAT3 Research and Development Plan within [***] after AstraZeneca's receipt of such Phase 1/2 Trial Data Package; and

(ii) If the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) and there is a Medium Response Outcome (and AstraZeneca does not plan to [***]), *provided* Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(i), AstraZeneca will initiate a Clinical Study within [***] after AstraZeneca's receipt of such Phase 1/2 Trial Data Package.

(h) **Subsequent [***] Development within [***] after a Medium Response Outcome**. If AstraZeneca pays Isis the milestone payment under Column 2 of TABLE 1 in Section 8.4 for a Medium Response Outcome, but initiates a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients within [***] after AstraZeneca's Initiation of a Clinical Study to evaluate ISIS-STAT3 $_{Rx}$ as a [***] in DLBCL Patients, then (A) within 30 days after AstraZeneca's receipt of an invoice from Isis, AstraZeneca will pay Isis an amount equal to $[***] ([***]), and (B) *so long as* AstraZeneca is developing or commercializing ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients (i) with respect to any unachieved milestone events, in lieu of paying Isis the milestone payments under Column 2 of TABLE 1 in Section 8.4, AstraZeneca will pay to Isis the milestone payments as set forth in

Column 1 of TABLE 1 in Section 8.4 when a milestone event listed in TABLE 1 is achieved by a STAT3 Product, and (ii) the High Response Outcome royalty rates set forth in Section 8.8 will apply to STAT3 Products.

(i) **Subsequent [***] Development more than [***] after a Medium Response Outcome**. If AstraZeneca pays Isis the milestone payment under Column 2 of TABLE 1 in Section 8.4 for a Medium Response Outcome but subsequently Initiates a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients *more than* [***] after AstraZeneca's Initiation of a Clinical Study to evaluate ISIS-STAT3$_{Rx}$ as a [***] in DLBCL Patients, then AstraZeneca will continue to pay Isis the milestone payments under Column 2 of TABLE 1 in Section 8.4, AstraZeneca will have no obligation to pay Isis such $[***] payment or the milestone payments as set forth in Column 1 of TABLE 1 in Section 8.4, and the High Response Outcome royalty rates set forth in Section 8.8 will not apply to STAT3 Products.

1.2.4. **Disputes Regarding High Response Outcome, Medium Response Outcome, Low Response Outcome, Safety Concern or Target Knock-Down**. If under Section 1.2.3(e) AstraZeneca timely disputes whether (i) a High Response Outcome, Medium Response Outcome or Low Response Outcome has been achieved (including whether the [***]), (ii) there is a Safety Concern, or (iii) Target Knock-Down was achieved, then the Parties will promptly (but no later than 15 days after the dispute arises) engage and refer such dispute to a mutually agreed upon single, independent Third Party oncologist with expertise in the area and appropriate professional credentials. Within 30 days of receiving the Phase 1/2 Trial Data Package, to the extent disputed by the Parties, such Third Party expert will determine whether there is a High Response Outcome, Medium Response Outcome, or Low Response Outcome and whether there is a Safety Concern, and/or if there is Target Knock-Down. The determination of the Third Party expert engaged under the preceding sentence will be final and binding on the Parties. The costs of any Third Party expert engaged under this Section 1.2.4 will be paid by the Party against whose position the Third Party expert's determination is made.

ARTICLE 2.
[***] RESEARCH AND DEVELOPMENT PROGRAM

2.1. **[***] Program Overview**. The intent of the [***] Program is (i) for Isis to discover a development candidate for [***] and complete IND-Enabling Toxicology Studies with such development candidate, and (ii) for AstraZeneca to perform, among other activities, *in vitro* and *in vivo* experiments to support the selection of the [***] Development Candidate, and all other preclinical, clinical, regulatory and commercial activities related to [***] Products. The purpose of this Section 2.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the [***] Research and Development Plan, and therefore

this Section 2.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

2.2. **[***] Research and Development Responsibilities**.

2.2.1. **[***] Research and Development Plan Activities; Timelines**. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under the [***] Research and Development Plan (which is attached hereto as APPENDIX 2) in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under the [***] Research and Development Plan in accordance with the timelines specified therein. In addition, with respect to the [***] Program:

(a) Isis will use Commercially Reasonable Efforts to designate an [***] Lead Candidate by [***]; and

(b) subject to Section 2.2.3 and Section 2.2.4, Isis will initiate IND-Enabling Toxicology Studies no later than [***] after AstraZeneca notifies Isis of the Selection of the [***] Development Candidate under Section 2.2.3.

2.2.2. **[***] Research and Development Plan.** The Parties will continue to develop and refine the [***] Research and Development Plan initially agreed at the Effective Date as needed, and update it at least once each six months, and submit it to the JSC for its review and comment. Subject to Section 4.1.4, any material changes to the [***] Research and Development Plan must be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. On a rolling basis, the [***] Research and Development Plan will contain activities for at least the next [***], including the key Development and regulatory decisions for the [***] Development Candidate and the key factors that will be considered when making such Development and regulatory decisions. In addition, once the [***] Development Candidate is selected under Section 2.2.3, the JSC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND and will specify that AstraZeneca will [***]. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 2.2.2.

2.2.3. **[***] Development Candidate**. Isis will use Commercially Reasonable Efforts to designate an [***] Lead Candidate by [***]. AstraZeneca shall be entitled to participate with Isis in the identification of an [***] Lead Candidate and a back-up and Isis will notify AstraZeneca in writing promptly after designating an [***] Lead Candidate and, together with such notice, Isis will provide AstraZeneca

the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] after AstraZeneca receives such Lead Candidate Data Package) (such [***] deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection

identification criteria analysis, the "[***] ***Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the [***] Lead Candidate (or another [***] Compound) as the [***] Development Candidate. In addition, during such [***] period, AstraZeneca will keep the JSC apprised of AstraZeneca's progress in making a decision regarding which [***] Compound AstraZeneca may select as the [***] Development Candidate to enable Isis to plan as early as possible for manufacturing of the [***] Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up [***] Compound(s) to the proposed [***] Lead Candidate should be considered alongside the proposed [***] Lead Candidate, then the JSC may unanimously agree to extend the [***] Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the [***] Development Candidate. If AstraZeneca selects the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate, then AstraZeneca will notify Isis of such selection by the [***] Development Candidate Decision Deadline, and will pay Isis the [***] Development Candidate milestone payment under Section 8.5 within 30 days after AstraZeneca's receipt of an invoice from Isis. Subject to Section 2.2.4, if AstraZeneca either (i) provides a written notice that it has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline or (ii) does not provide Isis any written notice as to whether or not AstraZeneca has selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline, then the license granted by Isis to AstraZeneca under Section 6.1.2 will terminate and no milestone payment for such [***] Development Candidate will be payable.

2.2.4. Failure to Designate an [***] Lead Candidate or Select an [***] Development Candidate.

(a) ***JSC Decides to Perform Additional Work***. If AstraZeneca has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline but AstraZeneca informs Isis that it believes further work to pursue an [***] Development Candidate should be pursued, then, within 30 days after the [***] Development Candidate Decision Deadline, the JSC may unanimously decide to pursue further work to identify other [***] Compounds for consideration as the [***] Development Candidate under a mutually agreed amended [***] Research and Development Plan, in which case the license granted by Isis to AstraZeneca under Section 6.1.2 will not terminate as provided in Section 2.2.3.

(b) ***Isis Fails to Designate an [***] Lead Candidate by [***]; the JSC Decides Not to Perform Additional Work***. If (A) Isis, having used

Commercially Reasonable Efforts, does not designate an [***] Lead Candidate by [***], or (B) Isis has designated an [***] Lead Candidate by [***], but AstraZeneca has not selected the [***] Lead Candidate or any other [***] Compound as the [***] Development Candidate by the [***] Development Candidate Decision Deadline and the JSC has not unanimously decided to pursue further work to identify other [***] Compounds for consideration as the [***] Development Candidate under a mutually agreed amended [***] Research and Development Plan, then, if AstraZeneca elects to abandon its rights to [***] and terminate the license granted by Isis to AstraZeneca under Section 6.1.2, no [***] milestone payment will be payable but AstraZeneca may elect to add an additional Oncology Target to the Oncology Collaboration by providing Isis written notice of such election (together with the gene target AstraZeneca proposes to add to the Oncology Collaboration, including the gene name and the NCBI accession number or nucleic acid sequence for such gene target, and any Patent Rights comprised in AstraZeneca Background IP consistent with the process described in Section 3.3.5 below) on or before (X) [***], in the case of item (A) above, or (Y) within [***] after the last to occur in item (B) above, as applicable. If AstraZeneca timely provides Isis with such an election notice, and Isis and AstraZeneca mutually agree on the proposed target, then, upon Isis' receipt of AstraZeneca's written agreement to be responsible for any Target Encumbrances that Isis notifies AstraZeneca as being applicable to such proposed target and related Products, (i) such proposed target will be an Oncology Target and the Oncology Collaboration will be expanded to a total of four Oncology Targets, (ii) Isis' obligations and AstraZeneca's rights under this Agreement with respect to the [***] Research and Development Plan (including the [***] Development Candidate and all other [***] Compounds) will terminate, and (iii) the license granted by Isis to AstraZeneca under Section 6.1.2 will terminate and no [***] milestone payment will be payable.

2.2.5. Notice of Completion of IND-Enabling Toxicology Studies; IND Support Package. Isis will notify AstraZeneca in writing within 30 days after Isis achieves Completion of the IND-Enabling Toxicology Studies under the [***] Research and Development Plan and, together with such notice, will deliver to AstraZeneca the IND Support Package.

ARTICLE 3.
ONCOLOGY COLLABORATION; OPTIONS

3.1. Oncology Collaboration Overview. The intent of the Oncology Collaboration is (i) for Isis to generate an Oncology Lead Candidate for each of the Oncology Collaboration Programs, (ii) with respect to each such Oncology Lead Candidate, for AstraZeneca to perform certain *in vitro* and *in vivo* (animal) experiments to support their designation,

and (iii) for AstraZeneca to conduct IND-Enabling Toxicology Studies with the Oncology Development Candidate. For each Oncology Collaboration Program, AstraZeneca will have an exclusive option to further develop and commercialize Products under an exclusive license from Isis. The purpose of this Section 3.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the Oncology Collaboration Programs, and therefore this Section 3.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below. Both Parties agree that while the primary focus of the collaboration is oncology, if the JSC unanimously agrees, then targets outside oncology could be included in this Agreement either during the selection process described below or as Substituted Targets.

3.2. Oncology Research and Development Plan Activities and Term.

3.2.1. Oncology Research and Development Plan Activities; Timelines. Each Oncology Research and Development Plan will be mutually agreed to by the Parties, and subject to Section 4.1.4 any material changes to a Collaboration Plan will be mutually agreed to by the Parties in accordance with the provisions of Section 4.1.3. Isis will use Commercially Reasonable Efforts to conduct the Isis Conducted Activities designated under each Oncology Research and Development Plan in accordance with the timelines specified therein, and AstraZeneca will use Commercially Reasonable Efforts to conduct the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan in accordance with the timelines specified therein. In addition Isis will use Commercially Reasonable Efforts to designate an Oncology Lead Candidate with respect to a particular Oncology Target. Both Parties will use their Commercially Reasonable Efforts to agree to the Reserved Targets in accordance with the timelines in Section 3.3.5 and to designate the Oncology Targets in accordance with the timelines in Section 3.3.6.

3.2.2. Oncology Collaboration Term. The period during which the Parties will conduct the Oncology Collaboration (such period, the "***Oncology Collaboration Term***") will begin on the Effective Date and will end on the [***] anniversary of the Effective Date; *provided that* if one or both Substitute Targets are substituted into the Oncology Collaboration in accordance with Section 3.3.7 below or an additional Oncology Target is added to the Oncology Collaboration in accordance with Section 2.2.4, then, in order to provide sufficient time to perform such additional activities with respect to such Substitute Target or additional Oncology Target, the Oncology Collaboration Term for all Oncology Collaboration Programs will be extended for an additional [***] from the date the last Substitute Target or additional Oncology Target was included in the Oncology Collaboration.

3.3. Oncology Collaboration.

3.3.1. Oncology Research and Development Plans. The Oncology Collaboration

will be carried out in accordance with a written research and development plan that sets forth all research and development activities of the Parties with respect to each Oncology Target through AstraZeneca's Completion of the IND-Enabling Toxicology Studies (each such plan, an "***Oncology Research and Development Plan***"). Each time the Parties have designated one of the three Oncology Targets in accordance with Section 3.3.6, the JSC will unanimously agree on an Oncology Research and Development Plan for each such Oncology Target. Each Oncology Research and Development Plan will include a description of the specific activities to be performed by the Parties in support of the Oncology Collaboration Program, the specific criteria to achieve Target Sanction status for the Oncology Target, the specific activities to be performed to achieve an Oncology Development Candidate and projected timelines for completion of such activities. A template Oncology Research and Development Plan for guidance on the expected activities of each Party is attached hereto as APPENDIX 3, which will be used by the JSC as a starting point when creating each Oncology Research and Development Plan. The Parties will continue to develop and refine each Oncology Research and Development Plan initially agreed as needed, and update it at least once every six months, and submit it to the JSC for its review and comment. AstraZeneca will ensure on a rolling basis that each Oncology Research and Development Plan contains activities for at least the next [***], including the key Development and regulatory decisions for the Oncology Development Candidate and the key factors that will be considered when making such Development and regulatory decisions, and will be consistent in scope with the STAT3 Research and Development Plan and [***] Research and Development Plan. For clarity, Isis will not be obligated to initiate work on more than [***] Oncology Targets (excluding a Substitute Target) in any rolling [***] period during the Oncology Collaboration Term to ensure even utilization of resources unless agreed otherwise unanimously by the JSC. Lastly, once an Oncology Development Candidate is selected under Section 3.3.3, the JSC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND and will specify that AstraZeneca will reimburse Isis for its time incurred in performing Isis' designated responsibilities in connection with the IND filing to the extent those responsibilities are not Isis Conducted Activities, at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis in performing such activities agreed in advance by AstraZeneca. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to allocate such [***] to the activities to be performed by Isis pursuant to this Section 3.3.1.

3.3.2. Target Sanction. The JSC will determine if an Oncology Target has achieved Target Sanction status based on the specific criteria determined by the JSC. The JSC will record in the minutes of the JSC each time an Oncology Target

has achieved Target Sanction status.

3.3.3. Oncology Development Candidate Selection. Isis will notify AstraZeneca in writing promptly after designating an Oncology Lead Candidate and, together with such notice, Isis will provide AstraZeneca the applicable Lead Candidate Data Package. As promptly as possible (but no later than [***] after AstraZeneca receives such Lead Candidate Data Package) (each such [***] deadline, which AstraZeneca has determined is sufficient for AstraZeneca to complete its candidate selection identification criteria analysis, an "***Oncology Development Candidate Decision Deadline***"), AstraZeneca will determine whether to select the Oncology Lead Candidate (or another Oncology Compound) as an Oncology Development Candidate. In addition, during such [***] period, AstraZeneca will keep

the JSC apprised of AstraZeneca's progress in making a decision regarding which Oncology Compound AstraZeneca may select as the Oncology Development Candidate to enable Isis to plan as early as possible for manufacturing of the Oncology Development Candidate for IND-Enabling Toxicology Studies. If the JSC determines that any back up Oncology Compound to the proposed Oncology Lead Candidate should be considered alongside the proposed Oncology Lead Candidate, then the JSC may unanimously agree to extend the Oncology Development Candidate Decision Deadline if the JSC determines AstraZeneca should have additional time to consider both candidates before making a decision as to which may be selected as the Oncology Development Candidate. If AstraZeneca selects the Oncology Lead Candidate or any other Oncology Compound as an Oncology Development Candidate, then AstraZeneca will notify Isis of such selection by the Oncology Development Candidate Decision Deadline, and will pay Isis the Designation of Oncology Development Candidate milestone payment under Section 8.6 within 30 days after AstraZeneca's receipt of an invoice from Isis. In addition, provided Isis has supplied the API to AstraZeneca in accordance with Section 4.6.1(b)(iii), AstraZeneca will initiate IND-Enabling Toxicology Studies under the applicable Oncology Research and Development Plan no later than [***] days after AstraZeneca pays Isis the Designation of Oncology Development Candidate milestone payment under Section 8.6.

If AstraZeneca either (i) does not provide Isis written notice that AstraZeneca has selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, or (ii), provides Isis written notice that AstraZeneca has not selected the Oncology Lead Candidate or any other Oncology Compound as the Oncology Development Candidate by the Oncology Development Candidate Decision Deadline, then such Oncology Collaboration Program will no longer be a part of this Agreement and AstraZeneca's Option for (and Isis' obligations with respect to) such Oncology Collaboration Program will terminate and no milestone payments for such Oncology Collaboration Program will be payable.

3.3.4. **Notice of Completion of IND-Enabling Studies; IND Support Package**. AstraZeneca will notify Isis in writing within 30 days after each time Completion of the IND-Enabling Toxicology Studies is achieved under an applicable Oncology Research and Development Plan and, together with such notice, will deliver to Isis the applicable IND Support Package, always provided that the Parties may mutually agree that an IND-Enabling Toxicology Study should not be completed (for example if there is an unacceptable toxicity in the study).

3.3.5. **Reserved Targets**. The Parties will select certain gene targets to be reserved (each such reserved gene target, a "***Reserved Target***") for potential selection as Oncology Targets under this Agreement according to the following schedule:

(a) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a pool of [***] oncology gene targets to be reserved for selection of the first Oncology Target under this Agreement;

(b) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a second pool of [***] oncology gene targets to be reserved for selection of the second Oncology Target under this Agreement; and

(c) Within [***] after the Effective Date, Isis and AstraZeneca will mutually agree on a third pool of [***] oncology gene targets to be reserved for selection of the third Oncology Target under this Agreement.

As part of the process for determining which gene targets will be reserved as Reserved Targets for potential selection as Oncology Targets, during the relevant time periods described above during which the Parties will consider gene targets to be Reserved Targets, AstraZeneca will inform Isis (A) if any of AstraZeneca's JSC or JPC members have knowledge (without conducting any additional investigation) of any additional Third Party licenses or other intellectual property rights that AstraZeneca requires in order for AstraZeneca to conduct its obligations under the Collaboration Plans if such Reserved Target was selected as an Oncology Target, and (B) if any Patent Rights comprised in AstraZeneca Background IP relate to any proposed gene targets, and whether AstraZeneca has the ability to grant a license or sublicense hereunder to such Patent Rights without violating the terms of any agreement with any Third Party. If AstraZeneca reports any of the conditions set forth in (A) or (B) of this Section 3.3.5(c) exist, then unless otherwise agreed by the Parties, such gene target will not be reserved as a Reserved Target for potential selection as an Oncology Target. Within [***] days after the Parties agree upon each pool of [***] Reserved Targets, Isis will inform AstraZeneca of any known encumbrances related to the Reserved Targets under any Third Party agreement to which Isis or its Affiliate is a party, including any payment obligations such as milestone and royalty payments (such encumbrances for which AstraZeneca is so notified, the "***Target Encumbrances***"). The JSC will maintain the list of Reserved Targets and will attach to the minutes of the JSC meeting any changes to such list of Reserved Targets.

3.3.6. **Selection of the Three Oncology Targets**. Within [***] after a designation of a pool of [***] Reserved Targets under Section 3.3.5, Isis and AstraZeneca will mutually agree on and designate one Reserved Target to be an Oncology Target that is the subject of an Oncology Collaboration Program. After selecting the Oncology Target, the remaining [***] unselected Reserved Targets will no longer be Reserved Targets, and Isis' obligations and AstraZeneca's rights under this Agreement with respect to such Reserved Targets (including but not limited to Section 5.1) will terminate. AstraZeneca will be responsible for any payment obligations arising from the Target Encumbrances identified in accordance with Section 2.2.4(b), Section 3.3.5 or Section 3.3.7 (other than Isis Supported Pass-Through Costs) applicable to such Oncology Targets and related Products. If Isis fails to notify AstraZeneca of a Target Encumbrance in accordance with Section 2.2.4(b), Section 3.3.5 or Section 3.3.7, such un-notified Target Encumbrance shall remain the responsibility of Isis. For clarity, this process will occur [***] times to nominate the [***] Oncology Targets and be complete no later than [***] from the Effective Date, and is illustrated in SCHEDULE 3.3.6, after which any remaining Reserved Targets will no longer be Reserved Targets.

3.3.7. **Rights of Substitution**.

(a) **Generally**. At any time during the first [***] years of the Oncology Collaboration Term, AstraZeneca will have the right, subject to the limits set forth below, to propose that research and development activities be discontinued with respect to an Oncology Target for which [***] (a "***Discontinued Target***"), and to propose that a new oncology target be substituted for such Discontinued

Target in accordance with the procedures set out below in Section 3.3.7(b) (such notice, a "***Substitute Notice***" and such newly proposed oncology target, a "***Proposed Substitute Target***").

(b) **Proposing the Substitute Target**. Within 30 days after Isis' receipt of a Substitute Notice, Isis and AstraZeneca will discuss and mutually agree whether such Proposed Substitute Target will become an Oncology Target. Isis will, within [***] days after Isis' receipt of any Substitute Notice, inform AstraZeneca of any Target Encumbrances applicable to the Proposed Substitute Target. If Isis and AstraZeneca mutually agree that the Proposed Substitute Target will become an Oncology Target, then such Proposed Substitute Target (a "***Substitute Target***") will become an Oncology Target upon (i) Isis' receipt of AstraZeneca's written agreement to be responsible for any payment obligations arising from the Target Encumbrances identified in accordance with this Section 3.3.7(b) (other than Isis Supported Pass-Through Costs) applicable to such Substitute Target and related Products, and (ii) if the Substitute Target is substituted in as an Oncology Target after the Discontinued Target achieved Target Sanction status, Isis' receipt of the payment in accordance with Section

3.3.7(d) below. For clarity, any Discontinued Target will no longer be an Oncology Target and will therefore no longer be a part of the Oncology Collaboration under this Agreement, and Isis' obligations and AstraZeneca's rights under this Agreement with respect to such Discontinued Target (including but not limited to Section 5.1.1) will terminate.

(c) **Number of Substitute Targets**. Notwithstanding anything to the contrary contained in this Agreement, in no event will AstraZeneca have the right to designate more than [***] Substitute Targets under this Section 3.3.7; *provided that* no more than [***] of such [***] Substitute Targets can be substituted in for an Oncology Target that has reached [***] status.

(d) **Payment for the Substitute Target**. If a Substitute Target is substituted in as an Oncology Target after [***] status for a Discontinued Target under this Section 3.3.7, AstraZeneca will pay Isis $[***] within 30 days after such Substitute Target is substituted in as an Oncology Target.

3.3.8. **Oncology Research and Development Plans**. If a Substitute Target is substituted in under Section 3.3.7, within 30 days after such substitution the Parties will mutually agree on an Oncology Research and Development Plan for such new Oncology Target using the template Oncology Research and Development Plan attached hereto as APPENDIX 3 as a starting point, subject to review and comment by the JSC, and remove any Oncology Research and Development Plan with respect to the Discontinued Target.

3.4. **Expiration of Oncology Collaboration Term**. On an Oncology Collaboration Program-by-Oncology Collaboration Program basis, if, despite the Parties' Commercially Reasonable Efforts, by the expiration of the Oncology Collaboration Term, Isis has not designated an Oncology Lead Candidate with respect to a particular Oncology Target, then (i) the Parties' will no longer have an obligation to perform any activities under this ARTICLE 3 with respect to such Oncology Collaboration Program; (ii) any Oncology Collaboration Program that has not reached the Development Candidate stage will no longer be considered an Oncology Collaboration Program and the applicable gene target associated therewith will no longer be an Oncology Target under this Agreement; (iii) the Parties' respective obligations and AstraZeneca's rights under this Agreement with respect to such Oncology Target and any Compounds targeting such Oncology Target will then terminate, and Isis will be free to Develop and Commercialize on its own or with a Third Party such Oncology Target and any ASOs targeting such Oncology Target; (iv) Isis will have exclusive rights (and AstraZeneca will, and hereby does grant Isis an exclusive license) to all data, results and information generated under the Oncology Collaboration Program for such Oncology Target to research, develop, manufacture and commercialize ASOs targeting such Oncology Target and AstraZeneca will promptly transfer to Isis copies of all such data, results and information in AstraZeneca's possession, provided that if within five years after the expiration of the Oncology Collaboration Term for such Oncology Target, Isis is not Developing ASOs for such Oncology Target, such rights and license shall become non-

exclusive and (v) AstraZeneca will and hereby does grant Isis an irrevocable, royalty free non exclusive license to any Know-How and/or Patent Rights generated by AstraZeneca under the Oncology Collaboration Program for such Oncology Target to research, develop, manufacture and commercialize ASOs targeting such Oncology Target. With regard to the Jointly-Owned Collaboration Technology for such Oncology Collaboration Program, Isis will control the Jointly-Owned Patents that result, and AstraZeneca will assign ownership to Isis on condition that Isis grants AstraZeneca an irrevocable, royalty-free, non-exclusive license for any purpose. For clarity, except to the extent expressly set forth in the foregoing, the expiration of the Oncology Collaboration Term will not affect the Parties' respective rights and obligations with respect to any Oncology Collaboration Program that has reached the Development Candidate stage by the end of the Oncology Collaboration Term and for which AstraZeneca has timely exercised its Option under Section 3.5.

3.5. **Options**. On an Oncology Target-by-Oncology Target basis, AstraZeneca has an exclusive option which it may exercise at any time on or before 5:00 p.m. (Pacific time) on the [***] day (each, an "***Option Deadline***") following the earlier of (i) [***], or (ii) [***] (each, an "***Option***") to obtain from Isis the license set forth in Section 6.1.3 below. AstraZeneca will notify Isis whether AstraZeneca is exercising its Option to license the applicable Oncology Target (and all Products included in the applicable Oncology Collaboration Program) by notifying Isis in writing on or before the applicable Option Deadline.

3.5.1. If AstraZeneca notifies Isis in writing by the Option Deadline that AstraZeneca is exercising the Option, AstraZeneca shall pay Isis the license fee set forth in Section 8.2 within 30 days after AstraZeneca's receipt of an invoice from Isis for such license fee, and Isis will, and hereby does, grant to AstraZeneca the license set forth in Section 6.1.3 below.

3.5.2. If AstraZeneca either (i) notifies Isis in writing by the Option Deadline that AstraZeneca is not exercising the Option, or (ii) does not provide any written notice to Isis by the Option Deadline as to whether or not AstraZeneca is exercising the Option, then AstraZeneca's Option will expire and no license fee is payable under Section 8.2 with respect to such Option. In such a case, AstraZeneca will have no further rights to (and Isis will have no further obligations with respect to) such Oncology Target (including all Compounds included in the applicable Oncology Collaboration Program) and the gene target to which such Compounds are directed will no longer be an

Oncology Target. Following any expiration of an Option under this Section 3.5.2, subject to agreeing otherwise as provided in Section 3.3.4, AstraZeneca will [***] and, upon [***], will promptly transfer to Isis all data, results and information related to the testing and studies with respect to the applicable Oncology Target in the possession of AstraZeneca and its contractors.

ARTICLE 4.
COLLABORATION MANAGEMENT; ADMINISTRATION; COSTS AND EXPENSES AND MANUFACTURING

4.1. Collaboration Management.

4.1.1. JSC. The Parties will establish a joint steering committee ("***JSC***") for the STAT3 Program, [***] Program, and the Oncology Collaboration Programs, to provide advice and make recommendations on the conduct of activities under the respective Collaboration Plans, which advice and recommendations will be consistent with each Collaboration Plan. The JSC will consist of three representatives appointed by Isis and three representatives appointed by AstraZeneca. Each JSC member will be a senior development leader or have similar experience and expertise as a senior development leader. Each Party will designate one of its three representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of each JSC. The co-chairs will be responsible for overseeing the activities of its JSC consistent with the responsibilities set forth in Section 4.1.2. SCHEDULE 4.1.1 sets forth certain JSC governance matters agreed to as of the Effective Date. The JSC will determine the JSC operating procedures at its first meeting, including the JSC's policies for replacement of JSC members, policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JSC meetings.

4.1.2. Role of the JSC. Without limiting any of the foregoing, the JSC will perform the following functions, some or all of which may be addressed directly at any given JSC meeting:

(a) Maintain the list of Reserved Targets;

(b) Maintain the list of Oncology Targets that are the subject of the Oncology Collaboration Programs;

(c) Set the Target Sanction criteria for each Oncology Target;

(d) Consider whether and for how long a back up candidate for the [***] Lead Candidate or the Oncology Lead Candidate shall be considered in parallel with the [***] Lead Candidate or Oncology Lead Candidate (as applicable).

(e) Create each Oncology Research and Development Plan using the template attached hereto as APPENDIX 3 as a starting point;

(f) review the overall progress of the activities under the applicable Collaboration Plan, including forecasts of costs associated with supplies of API/finished Product;

(g) review and provide advice on the applicable Collaboration Plan;

(h) subject to Section 4.1.3(a), materially amend the applicable Collaboration Plan upon unanimous consent; and

(i) such other review and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement.

4.1.3. Collaboration Program Decision Making.

(a) AstraZeneca shall have the final decision making authority with respect to amendments to a Collaboration Plan which are not material as provided in Section 4.1.3(b).

(b) A proposed amendment to a Collaboration Plan shall be regarded as material for the purposes of this Section 4.1.3 if it would result in either (i) [***], or (ii) [***].

(c) If a proposed material amendment to a Collaboration Plan cannot be unanimously agreed to by the JSC or the Parties and the change could be materially detrimental to the further development of a Product then the co-chairs shall continue to revise the Collaboration Plan until such time as a unanimous decision can be reached, and at any time either Party may refer the matter to the Senior Representatives in accordance with Section 14.1, which Senior Representatives shall be asked to use their good faith efforts to mutually agree on an acceptable way forward. Once the matter has been referred to the Senior Representatives, if after negotiating in good faith pursuant to Section 14.1.1, undertaken with reasonable promptness and including a detailed comparison of the proposed amendment to the Collaboration Plan against the AstraZeneca performance metrics described in the document provided by AstraZeneca to Isis entitled [***] attached hereto as SCHEDULE 4.1.3(c), the Senior Representatives fail to reach an amicable agreement within 90 days, then AstraZeneca shall have the final decision making authority (1) if [***], or (2) if [***], or (3) if [***].

(d) ***"Initial Research and Development Plan"*** means, as applicable (i) the STAT3 Research and Development Plan or [***] Research and Development Plan (as each such plan is attached to this Agreement on the Effective Date) or (ii) with respect to each Oncology Development Candidate, the first Oncology Research and Development Plan agreed to by the Parties following designation of such Oncology Development Candidate.

(e) Isis and AstraZeneca will conduct the Collaboration Plans giving due consideration to the recommendations and advice of the JSC, in accordance with their obligations under Section 1.2.1, Section 2.2.1 and Section 3.3.1. With respect to the STAT3 Research and Development Plan, [***] Research and Development Plan and each Oncology Research and Development Plan agreed to by the Parties following designation of the applicable Oncology Development Candidate, AstraZeneca will have the final decision-making authority regarding the [***], and [***].

(f) Notwithstanding the foregoing, in all cases where AstraZeneca has final decision making authority Isis will have no obligation to perform any activity that (A) [***], (B) [***], or (C) [***].

4.1.4. **Term of the JSC**. Isis' obligation to participate in relation to a Collaboration Plan in the JSC will terminate on the date Isis completes all the Isis Conducted Activities under such Collaboration Plan. Thereafter, Isis will have the right, but not the obligation, to participate in the JSC meetings in relation to such Collaboration Plan upon Isis' request. After the [***] for a Product specified in the Collaboration Plan, in respect of such Collaboration Plan, the JSC shall cease to be responsible for making decisions (and for the avoidance of doubt, without limiting the foregoing, the provisions of Section 4.1.3 shall cease to apply) and AstraZeneca shall have full decision making authority and may make amendments to such Collaboration Plan (including with respect to the [***] program under such Collaboration Plan), subject to AstraZeneca's continuing obligation to use Commercially Reasonable Efforts under this Agreement; *provided, however*, that, with respect to the [***] for such Product, AstraZeneca's decision making will be consistent with the Collaboration Plan approved by the JSC at the time such [***] (taking into consideration [***]). The JSC shall become a forum for the Parties to share information regarding the Collaboration Plan and the Product, and the Parties shall decide on the number and frequency of meetings required of the JSC in respect of such Collaboration Plan in its new role.

4.2. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JSC and performing the activities listed in SCHEDULE 4.2.

4.3. **Disclosure of Results**. Each Party will promptly disclose to the other Party the results of all work performed by the Parties under the Collaboration Plans in a reasonable manner as such results are obtained. Isis and AstraZeneca will provide reports and analyses at each JSC meeting, and more frequently on reasonable request by the JSC, detailing the current status of each Collaboration Plan. The results, reports, analyses and other information regarding the Collaboration Plans disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports required, excluding reports

needed for submission to a Regulatory Agency, under this Section 4.3 may take the form of and be recorded in minutes of the JSC that will contain copies of any slides relating to the results and presented to the JSC. Reports needed to support regulatory submissions and updates to a Regulatory Agency will be provided in a timely manner and in a format consistent with industry practice as agreed upon by the JSC.

4.4. **Materials Transfer**. In order to facilitate the activities under the Collaboration Plans, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration Plans. All such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

4.5. **Collaboration Costs and Expenses**.

4.5.1. **STAT3 Program and [***] Program.**

(a) **R&D Research and Development Plan Costs**. Except as otherwise provided below and under Section 4.5.1(b), Isis will be responsible for all costs and expenses associated with the Isis Conducted Activities designated under the R&D Research and Development Plan, and AstraZeneca will be responsible for all costs and expenses associated with any AstraZeneca Conducted Activities designated under the R&D Research and Development Plan. With respect to the [***] Program, Isis will be responsible for providing API to AstraZeneca in accordance with Section 4.6.1.

(b) **Other STAT3 Program and [***] Program Costs**.

(i) **Under the R&D Research and Development Plan**. AstraZeneca will be responsible for paying Isis any costs and expenses associated with Isis' regulatory support and safety reporting work for the [***] ([***]) and, in accordance with Section 4.6.1, the cost of the API and finished Product for the [***]. In addition, AstraZeneca will be responsible for paying as a lump sum any Additional Plan Costs resulting from AstraZeneca-Initiated Changes. Isis will permit AstraZeneca to review and approve the Additional Plan Costs before implementing any AstraZeneca-Initiated Changes. Isis and AstraZeneca will update the R&D Research and

Development Plan with any such revised studies and Isis will invoice AstraZeneca for any such approved Additional Plan Costs within 30 days after such Additional Plan Costs are approved. AstraZeneca will pay the invoices submitted pursuant to this Section 4.5.1(b)(i) for such [***]-related work costs and approved Additional Plan Costs within 30 days after AstraZeneca's receipt of the applicable invoice.

(ii) **Generally**. Except as otherwise provided under this Section 4.5.1, AstraZeneca will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of STAT3 Products and [***] Products, including the AstraZeneca Conducted Activities.

4.5.2. Oncology Collaboration Program Costs and Expenses.

(a) **Oncology Research and Development Plan Costs Paid by Isis**. Until AstraZeneca exercises the Option for a particular Oncology Collaboration Program, except as otherwise provided under Section 3.3.4 or Section 4.5.2(b), Isis will be responsible for all costs and expenses associated with the Isis Conducted Activities designated under each Oncology Research and Development Plan and AstraZeneca will be responsible for all costs and expenses associated with the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan. With respect to each Oncology Collaboration Program, Isis will be responsible for providing API to AstraZeneca in accordance with Section 4.6.1.

(b) **Oncology Research and Development Plan Costs Paid by AstraZeneca**.

(i) **Before Option Exercise**. Before Option exercise, AstraZeneca will be responsible for all costs and expenses associated with the AstraZeneca Conducted Activities designated under each Oncology Research and Development Plan. In addition, AstraZeneca will be responsible for paying as a lump sum any Additional Plan Costs resulting from AstraZeneca-Initiated Changes. Isis will permit AstraZeneca to review and approve the Additional Plan Costs before implementing any AstraZeneca-Initiated Changes. Isis and AstraZeneca will update the applicable Oncology Research and Development Plan with any such revised studies and Isis will invoice AstraZeneca for any such approved Additional Plan Costs within 30 days after such Additional Plan Costs are approved. AstraZeneca will pay the invoices submitted pursuant to this Section 4.5.2(b)(i) for such approved Additional Plan Costs within 30 days after AstraZeneca's receipt of the applicable invoice.

(ii) **After Option Exercise**. After Option exercise, AstraZeneca will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products, including all AstraZeneca Conducted Activities.

4.6. Collaboration Manufacturing and Supply.

4.6.1. Supplies for Activities under the Collaboration Plans.

(a) **Isis Conducted Activities**. [***], Isis will supply API and finished Product sufficient to support the Isis Conducted Activities designated under a given Collaboration Plan, including but not limited to the API to support the IND Enabling Toxicology Studies for the [***] Program.

(b) **AstraZeneca Conducted Activities**. In addition, with respect to the AstraZeneca Conducted Activities, Isis will supply (the "***Initial Supply***"):

(i) ***STAT3 Program Supply***. API and finished Product sufficient to support the [***] that will be conducted by AstraZeneca under the STAT3 Research and Development Plan;

(ii) ***[***] Program Supply***. The quantity of API [***] (which will be set forth in the [***] Research and Development Plan) to support the [***] for the [***] Development Candidate; and

(iii) ***Oncology Programs***. The quantity of API [***] for each Oncology Development Candidate, and the quantity of API [***] (which will be set forth in the applicable Oncology Research and Development Plan) for each Oncology Development Candidate.

In each of the foregoing cases in this Section 4.6.1(b), AstraZeneca will pay Isis for such API and/or finished Product at [***], within 60 days after AstraZeneca's receipt of the applicable invoice. Other than the finished Product sufficient to support the [***] under the STAT3 Research and Development Plan, AstraZeneca is responsible for supplying finished Product for all AstraZeneca Conducted Activities. In addition, should AstraZeneca require additional API or research-grade Compound for the STAT3 Program or the [***] Program for pre-clinical studies in [***] not covered by the STAT3 or [***] Research and Development Plan or in connection with the Oncology Research and Development Plans, then, at AstraZeneca's reasonable request, Isis will use its reasonable endeavors to provide (A) such API to AstraZeneca at [***], or (B) such research-grade Compound for such [***] studies [***] of such Compound (and for any additional quantities of research-grade Compound, at [***].

It is intended that the API lot used for [***] under a given Collaboration Plan will be of sufficient size to also use in the [***] of the relevant Product.

(c) **Initial Supply Payment and Delivery Schedule**. The Parties will mutually agree on the respective delivery and payment schedule for the Initial Supply consistent with the applicable Collaboration Plan.

(d) **Manufacturing Services Agreement**. Each of the Parties agrees and acknowledges that a mutually agreed manufacturing services agreement ("***MSA***") is required to be put in place to govern the supply arrangements by Isis, which shall be negotiated in good faith between the Parties following the Effective Date. The Parties' objective is that the MSA shall be entered into within [***] after the Effective Date and shall include, amongst other appropriate and detailed provisions, the provisions set out in Schedule 4.6.1(d).

4.6.2. **After Isis Completes the Isis Conducted Activities**. Once Isis completes the Isis Conducted Activities designated under a given Collaboration Plan, in addition to the Initial Supply, Isis will sell to AstraZeneca, if AstraZeneca desires, any other inventory of cGMP API, finished Product and packaged clinical trial material in Isis' possession [***]. In addition, if requested by AstraZeneca, Isis will negotiate in good faith to provide:

(a) additional API supply for [***], and

(b) if AstraZeneca [***].

4.7. **Applicable Laws and Bioethics**. The Research to be conducted by each Party (including by its subcontractors) pursuant to this Agreement shall be carried out in good scientific manner, and in compliance with all Applicable Laws, as well as the AstraZeneca bioethics policy attached at SCHEDULE 4.7, to attempt to achieve efficiently and expeditiously the objectives of the applicable Collaboration Plan. In respect of any Isis Conducted Activities to be initiated after the Effective Date, Isis and AstraZeneca will mutually agree on [***] and, prior to award of the work, shall work together to secure compliance with AstraZeneca's bioethics policy. Where a [***], the Parties will discuss and agree whether such [***]. Insofar as the requirements of complying with such policy will result in additional [***] costs being charged to Isis for work [***] for Isis Conducted Activities, compared to [***], AstraZeneca agrees to be responsible for such additional costs [***]. The Parties will agree when such costs will be invoiced by Isis and AstraZeneca will pay such costs to Isis within 60 days after AstraZeneca's receipt of an invoice from Isis. The Parties' agreement under this Section 4.7 can be through the JSC.

ARTICLE 5.
EXCLUSIVITY COVENANTS

5.1. **Exclusivity Covenants**.

5.1.1. **Isis' and AstraZeneca's Exclusivity Covenants**. Except in the performance of its obligations under this Agreement and except as set forth in Section 5.1.2 or Section 5.1.3, on a Gene Target-by-Gene Target basis, Isis and AstraZeneca will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(a) ***STAT3 and [***]***. (A) The discovery, research or development of an ASO that is designed to bind to the RNA that encodes STAT3 or [***] in the Field until [***]; and (B) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes STAT3 or [***] in the Field until [***];

(b) ***Reserved Targets***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes any of the Reserved Targets, from the date each such oncology gene target becomes a Reserved Target under Section 3.3.5 until the date such Reserved Target ceases to be a Reserved Target by operation of Section 3.3.6;

(c) ***Oncology Targets During the Option Period***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes any Oncology Target, from the date each Oncology Target is agreed to by the Parties until the earlier of the date (y) AstraZeneca exercises the applicable Option for such Oncology Target, or (z) such Option expires unexercised or is terminated; and

(d) ***Oncology Targets After Option Exercise***. The discovery, research or development of an ASO that is designed to bind to the RNA that encodes an Oncology Target in the Field for which AstraZeneca has exercised its Option in accordance with this Agreement, (A) with respect to discovery, research or development of an ASO that is designed to bind to the RNA that encodes such Oncology Target, until [***], and (B) on a country by country basis with respect to commercialization of an ASO that is designed to bind to the RNA that encodes such Oncology Target in the Field, until [***].

5.1.2. **Isis Follow-On Products**. Notwithstanding the provisions of Section 5.1.1, on a Gene Target-by-Gene Target basis, if (A) AstraZeneca does not ask Isis to identify a follow-on product for a Gene Target by [***], or (B) Isis identifies a follow-on product for a Gene Target at AstraZeneca's request, but thereafter AstraZeneca does not use Commercially Reasonable Efforts to continue to develop and commercialize such follow-on compound, then Isis (for itself or with or for a Third Party) will be permitted to (i) discover, research and

develop an ASO designed to bind to the RNA that encodes such Gene Target that is not the Product being developed by AstraZeneca (an "***Isis Follow-On Product***"), and (ii) after [***] for a Product, commercialize an Isis Follow-On Product.

5.1.3. **Limitations and Exceptions to Each Party's [***] Rights**.

(a) **Exception and Limitations**. The Parties acknowledge and agree that, in addition to playing a role in cancer, the gene target, [***], is also known to potentially play a role outside of oncology (e.g., [***]), and therefore targeting [***] with an [***] ASO is a

possible approach for the treatment of non-oncology diseases. In exchange for AstraZeneca's agreement to not develop or commercialize an ASO targeting [***] for [***] and to not develop or commercialize an [***] for [***], Isis has agreed to [***] ASOs outside of [***] that [***].

Therefore, with respect to [***], the Parties memorialize the foregoing general principles by hereby agreeing to the following specific restrictions and limitations:

(i) **AstraZeneca's [***] Field**.

(1) ***[***]***. AstraZeneca does not have the right under Section 6.1.2 (nor does AstraZeneca have a license under Section 6.1.2 of this Agreement) to research, develop, manufacture, have manufactured, register, market and/or commercialize any ASO that is designed to bind to the RNA that encodes [***], for the diagnosis, prevention and/or treatment of [***].

(2) ***[***] and Other Indications***. AstraZeneca has the right under Section 6.1.2 (and has a license under Section 6.1.2 of this Agreement) to research, develop, manufacture, have manufactured, register, market and/or commercialize, on its own or with a Third Party (including granting an option or a license to a Third Party to do so), any ASO that is designed to bind to the RNA that encodes [***] for the diagnosis, prevention and/or treatment of:

a. ***[***]***. Any [***] disease in humans or animals for any [***] indication using any [***] ([***]); and

b. ***All Other Indications***. Any indications other than [***] and [***], using any [***] other than [***],

(such field described in this Section 5.1.3(a)(i), the "***AstraZeneca [***]-Field***").

(ii) **Isis' [***] Field**. Isis has the right (including to grant an option or a license to a Third Party) to research, develop, manufacture, have manufactured, register, market and commercialize, on its own or with a Third Party (including granting an option or a license to a Third Party to do so), any ASO that has all of the following attributes:

(1) is for the diagnosis, prevention and/or treatment of any disease in humans or animals other than for [***];

(2) [***];

(3) [***]; and

(4) [***] (each such [***] Compound, an "[***] ***Lead Compound***").

Each such [***] ASO Isis is permitted to exploit is an "***Isis [***]-Field ASO***," and the field described in this Section 5.1.3(a)(ii) is the "***Isis [***]-Field***."

(b) **Other Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 5.1.1 or Section 5.1.2:

(i) Performance of the Isis Conducted Activities;

(ii) Any activities permitted under the Prior Agreements as such agreements are in effect on the Effective Date and have been disclosed to AstraZeneca (and not as such Prior Agreements may be amended after the Effective Date); and

(iii) The granting of, or performance of obligations under, Permitted Licenses.

(c) **Other Limitations and Exceptions to AstraZeneca's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, AstraZeneca's performance of the AstraZeneca Conducted Activities will not violate Section 5.1.1 or Section 5.1.2.

Nothing in this ARTICLE 5 will require AstraZeneca to make any explicit statements on the [***] Product label in order to comply with AstraZeneca's obligations in Section 5.1.3(a)(i).

5.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes the Gene Targets in the Field, which are known to play a role in cancer. Isis and AstraZeneca are subject to exclusivity obligations under Section 5.1.1 and Section 5.1.2; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes a gene that is *not* a Gene Target (except, with respect to [***], Isis may do so with Isis [***]-Field ASOs) for any indication, even if such products are designed to treat cancer.

ARTICLE 6.
LICENSE GRANTS; TECHNOLOGY TRANSFER AND SUPPORT

6.1. License Grants to AstraZeneca.

6.1.1. STAT3 Development and Commercialization License. Subject to the terms and conditions of this Agreement, Isis hereby grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize STAT3 Products in the Field.

6.1.2. [***] Development and Commercialization License. Subject to the terms and conditions of this Agreement (including the provisions of Section 5.1.3(a)(i)), Isis hereby grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize [***] Products in the Field.

6.1.3. Oncology Target Development and Commercialization Licenses. On an Oncology Target-by-Oncology Target basis, subject to the terms and conditions of this Agreement, effective upon AstraZeneca's exercise of the Option for such Oncology Target in accordance with Section 3.5, Isis grants to AstraZeneca a worldwide, exclusive (including with regard to Isis and its Affiliates), royalty-bearing, sublicensable (in accordance with Section 6.1.4 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 6.1.4 below), register, market and Commercialize Oncology Products in the Field.

6.1.4. Sublicense Rights.

(a) Right to Grant Sublicenses. Subject to the terms and conditions of this Agreement, AstraZeneca will have the right to grant sublicenses through multiple tiers of sublicenses under the licenses granted under Section 6.1.1, Section 6.1.2 and Section 6.1.3 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents and Isis Know-How to an Affiliate of AstraZeneca or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How solely to (y) an Affiliate of AstraZeneca or (z) a Third Party with a valid license granted by Isis under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to manufacture Products in a manufacturing facility owned or operated by such Third Party (each, a "***Licensed CMO***");

provided that each such sublicense is for the continued development, manufacture and/or commercialization of a Product, and is subject to, and consistent with, the terms and conditions of this Agreement. AstraZeneca shall use reasonable efforts to ensure that all Persons to which it grants sublicenses comply with such terms and conditions.

(b) Enforcing Sublicense Agreements. If, within [***] days after first learning of any breach of such sublicense terms, AstraZeneca fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 6.1.4, which failure, in Isis' good faith determination, could cause [***], AstraZeneca hereby grants Isis the right to enforce such sublicense terms on AstraZeneca's behalf and will cooperate with Isis (which cooperation will be at AstraZeneca's sole expense and will include, AstraZeneca joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. AstraZeneca will provide Isis with written notice of any sublicense granted pursuant to this Section 6.1.4 that grants a Third Party rights to commercialize or manufacture a Product, within 30 days after the execution thereof, and if requested by Isis, a true and complete copy of any such sublicense or any sublicense that is the subject of a breach of terms sublicensed under this Agreement within 10 days of Isis' request, subject to AstraZeneca being entitled to make appropriate redaction for commercially sensitive information provided it is not relevant to enforcement or is not reasonably necessary for Isis to determine AstraZeneca's compliance with the terms of this Agreement.

(c) Requests to Grant Sublicenses to CMOs. In addition, if AstraZeneca provides Isis with a written request that Isis grant a license under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to a CMO designated by AstraZeneca that is not a Licensed CMO, solely for such CMO to manufacture Products for AstraZeneca, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, Isis will offer to grant such a license to such CMO on terms that are substantially similar to the terms Isis has previously agreed to with its Licensed CMOs.

(d) Effect of Termination on Sublicenses. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by AstraZeneca; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by AstraZeneca, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by AstraZeneca. AstraZeneca agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

(e) **Master Services Agreements and Material Transfer Agreements**. This Section 6.1.4 is not intended to require AstraZeneca to amend the standard terms and conditions of a master services agreement with a Third Party in place as of the Effective Date to conduct preclinical and/or clinical research and development on AstraZeneca's behalf, or material transfer agreements with academic collaborators or non-profit institutions, entered into after the Effective Date by AstraZeneca in connection with the Licensed Technology. However, after the Effective Date such agreements shall be subject to the approval of Isis for so long as Isis had decision making authority on the JSC, such approval not to be unreasonably withheld or delayed.

6.1.5. **Consequence of Natural Expiration of this Agreement**. On a Product-by-Product basis, if with respect to a particular Product this Agreement expires (i.e., is not terminated early) in a particular country in accordance with Section 12.1 then, in addition to the terms set forth in Section 12.3.1(c), Section 12.3.1(e), Section 12.3.1(f) and Section 12.3.1(g), Isis will and hereby does grant to AstraZeneca a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Licensed Know-How to Manufacture, Develop and Commercialize the Product that is the subject of such expiration in such country.

6.1.6. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to AstraZeneca under this Agreement are hereby retained by Isis or its

Affiliates. All rights in and to AstraZeneca Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by AstraZeneca or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

6.1.7. **License Conditions; Limitations**. Subject to Section 8.9, the licenses granted under Section 6.1.1, Section 6.1.2 and Section 6.1.3 and the sublicense rights under Section 6.1.4 are subject to and limited by (i) any applicable Target Encumbrances, (ii) in respect of the licenses granted under Section 6.1.1 and Section 6.1.2, the Prior Agreements as such agreements are in effect on the Effective Date and have been disclosed to AstraZeneca (and not as such Prior Agreement may be amended after the Effective Date), (iii) the Isis In-License Agreements as such agreements are in effect on the Effective Date (and not as such Isis In-License Agreements may be amended after the Effective Date); and (iv) the granting of, or performance of obligations under, Permitted Licenses.

6.1.8. **Trademarks for Products**. To the extent that (i) Isis owns any trademark(s) specific to a Product licensed under Section 6.1.1, Section 6.1.2 or Section 6.1.3, and (ii) AstraZeneca reasonably believes such trademark(s) are necessary or useful for such Product, then upon AstraZeneca's request and at AstraZeneca's sole cost and expense, Isis will assign its rights and title to such trademark(s) to AstraZeneca sufficiently in advance of the First Commercial Sale of a Product. Other than any such trademarks, AstraZeneca is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 6.1.1, Section 6.1.2 or Section 6.1.3.

6.1.9. **[***]**

6.2. **License Grant to Conduct the Isis and AstraZeneca Conducted Activities**.

6.2.1 As of the Effective Date, AstraZeneca hereby grants to Isis a worldwide, co-exclusive, royalty-free, fully paid up, license (with the right to sublicense to Third Parties solely to perform the Isis Conducted Activities) under the (i) Licensed Technology licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, and (ii) the AstraZeneca Technology, in each case for the sole purpose of Isis performing the Isis Conducted Activities under this Agreement.

6.2.2 On an Oncology Target-by-Oncology Target basis, as of the Effective Date and until the Option Deadline, Isis hereby grants to AstraZeneca a worldwide, non-exclusive, royalty-free, license (with the right to sublicense to Third Parties solely to perform the AstraZeneca Conducted Activities) under the Licensed Technology for the sole purpose of AstraZeneca performing the AstraZeneca Conducted Activities under this Agreement.

6.3. **Assignment of Isis Product-Specific Patents; Grant Back to Isis**.

6.3.1. On a Gene Target-by-Gene Target basis, with respect to any Gene Target for which AstraZeneca has an exclusive license under Section 6.1.1, Section 6.1.2 and Section 6.1.3, at AstraZeneca's request at any time after completion of the first Phase 2 Trial for the applicable Product, after discussion at the JPC, Isis will assign to AstraZeneca, Isis' ownership interest in:

(a) with respect to STAT3 Products or Oncology Products (as the case may be), all Isis Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties); and

(b) with respect to [***] Products, all Assignable [***] Product-Specific Patents within the Licensed Patents that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties).

6.3.2. AstraZeneca grants to Isis a worldwide, exclusive, sublicensable license under any Patent Rights assigned to AstraZeneca under Section 6.3.1 (i) for all purposes outside of the Field (except to license or Commercialize a compound from the STAT3, [***] or Oncology Product Specific Patents that specifically claim the STAT3 Product, [***] Product or Oncology Product being Developed and Commercialized by AstraZeneca), and (ii) to research, Develop, Manufacture, have Manufactured, register, market and Commercialize Isis Follow-On Products in accordance with Section 5.1.2, in each case to the extent permitted by this Agreement.

6.4. **Subcontracting**. Subject to the terms of this Section 6.4, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in this Agreement will

meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

6.5. **Technology Transfer**. After (i) the Effective Date, in the case of the Licensed Know-How licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, or (ii) on an Oncology Target-by-Oncology Target basis, the date the license under Section 6.1.3 is granted to AstraZeneca for such Oncology Target, Isis will deliver to AstraZeneca the following Licensed Know-How pursuant to a technology transfer plan to be mutually agreed by Isis and AstraZeneca:

6.5.1. **Licensed Know-How - Generally**. Copies of Licensed Know-How (other than the Isis Manufacturing and Analytical Know-How) in the Field in Isis'

possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, to AstraZeneca together with all regulatory documentation (including drafts) related to each Product (except that the [***]). To assist with the transfer of such Licensed Know-How, Isis will make its personnel reasonably available to AstraZeneca during normal business hours for up to [***] ([***]) of Isis' time to transfer such Licensed Know-How under this Section 6.5.1. Thereafter, if requested by AstraZeneca, Isis will provide AstraZeneca with a reasonable level of assistance in connection with such transfer, which AstraZeneca will reimburse Isis for its time incurred in providing such assistance at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

6.5.2. **Isis Manufacturing and Analytical Know-How**. Solely for use by AstraZeneca, its Affiliates or a Third Party acting on AstraZeneca's behalf to Manufacture API in AstraZeneca's own or an Affiliate's manufacturing facility, copies of the Isis Manufacturing and Analytical Know-How relating to Products in Isis' possession that has not previously been provided hereunder, which is necessary for the exercise by AstraZeneca, its Affiliates or a Third Party of the Manufacturing rights granted under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be. AstraZeneca will reimburse Isis for its time incurred in performing such technology transfer at the FTE rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca.

ARTICLE 7.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

7.1. **AstraZeneca Diligence**. Commencing on (i) the Effective Date, with respect to STAT3 Products and [***] Products licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2, and (ii) on an Oncology Target-by-Oncology Target and Product-by-Product basis, the date Isis grants AstraZeneca the license under Section 6.1.3 related to such Oncology Target, except for the Isis Conducted Activities that do not involve Additional Plan Costs, AstraZeneca is solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of Products.

7.1.1. **Integrated Development Plans**. AstraZeneca will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 and Section 6.1.3 through Approval as well as key aspects of worldwide regulatory

strategy, market launch, and Commercialization (each plan, an "***Integrated Development Plan***" or "***IDP***"). On a Product-by-Product basis, for each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, AstraZeneca will prepare the IDP no later than [***] for such Product, and the IDP will contain information consistent with AstraZeneca's Development and Commercialization plans for its similar products at similar stages of development. Once AstraZeneca has prepared such plans, AstraZeneca will update the IDP consistent with AstraZeneca's standard practice and provide such updates to Isis Annually. AstraZeneca and Isis will meet on a yearly basis to discuss the draft of the IDP and AstraZeneca will consider, in good faith, any proposals and comments made by Isis for incorporation in the final IDP. Notwithstanding the foregoing, on a Gene Target-by-Gene Target basis, AstraZeneca's obligations to provide Isis with information or reports under this Section 7.1.1 will terminate if Isis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes such Gene Target in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement.

7.1.2. **Investigator's Brochure**. Within 30 days after the Effective Date, Isis will provide to AstraZeneca the then current version of the Investigator's Brochure for ISIS-STAT3$_{Rx}$. AstraZeneca will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products licensed by AstraZeneca hereunder by providing updated versions of the Investigator's Brochure to Isis Annually and when Development of the Products results in any substantive change to the safety or risk to the Products. On a Product-by-Product basis, AstraZeneca's obligations under this Section 7.1.2 will terminate if Isis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes the Gene Target targeted by such Product in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement.

7.1.3. **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product (or, in the case of Isis as the invitee, that relate to Isis' antisense oligonucleotide platform), and will allow one representative of the invited Party to participate (as an observer) in any such meeting that is [***] (e.g., meetings regarding [***]) The costs associated with such

observer attendance will be met by the invitee Party, except if Isis' presence has been specifically requested by AstraZeneca, in which case AstraZeneca will reimburse Isis for its time incurred in attending at the FTE Rate. To the extent that AstraZeneca has not fully used the [***] available to it pursuant to Section 6.5.1 or Section 7.1.5, then AstraZeneca shall be entitled to

allocate such [***] to the activities to be performed by Isis pursuant to this Section 7.1.3.

7.1.4. **Regulatory Communications**. Each Party will provide the other Party with copies of documents and communications submitted to (including such drafts as the providing Party considers reasonably practicable but to include at least one pre finalization draft thereof) and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

7.1.5. **Assistance with Regulatory Filings**. On a Gene Target-by-Gene Target basis, following Lead Candidate designation for an applicable Gene Target, upon AstraZeneca's written request, Isis will assist AstraZeneca in preparing regulatory filings for the Products (including INDs and other regulatory filings for which AstraZeneca is the sponsor) and, except with respect to regulatory filing-related activities outlined in Section 7.1.3 and Section 7.1.4, such regulatory filings assistance will be [***]. Thereafter, upon AstraZeneca's written request, Isis will assist AstraZeneca in preparing regulatory filings for the Products at the FTE Rate, and any of Isis' reasonable travel expenses for travel requested by AstraZeneca, and any of its outside consultants' costs and consultants' reasonable travel expenses incurred by Isis agreed in advance by AstraZeneca. An estimate of such costs and expenses will be provided to AstraZeneca before initiation of agreed work.

7.1.6. **Class Generic Claims**. To the extent AstraZeneca intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or Isis' generation 2.0 or 2.5 chemistry platform(s), AstraZeneca will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

7.1.7. **Applicable Laws**. AstraZeneca will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

7.2. **Isis' Antisense Safety Database**.

7.2.1. Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, AstraZeneca will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by AstraZeneca and in the form in which AstraZeneca uses/stores such information for its own purposes, AstraZeneca will provide

Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products licensed by AstraZeneca under this Agreement as soon as practicable following the date such information is available to AstraZeneca (but not later than 30 days after AstraZeneca's receipt of such information). In connection with any reported serious adverse event, AstraZeneca will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, AstraZeneca will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within 30 days following the date such information is filed or is available to AstraZeneca, as applicable. Furthermore, AstraZeneca will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by AstraZeneca to Isis will be AstraZeneca Confidential Information; *provided*, *however*, that so long as Isis does not disclose the identity of a Product or AstraZeneca's identity, Isis may disclose any such AstraZeneca Confidential Information to (i) Isis' other partners pursuant to Section 7.2.2 below if such information is regarding class generic properties of ASOs, or (ii) any Third Party. AstraZeneca will deliver all such information to Isis for the Isis Internal ASO Safety Database to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). AstraZeneca will also cause its Affiliates and Sublicensees to comply with this Section 7.2.1.

7.2.2. From time to time, Isis utilizes the information in the Isis Internal ASO Safety Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Isis will promptly inform AstraZeneca of such issues and provide the data supporting Isis' conclusions.

7.3 **Pharmacovigilance; ISIS-STAT3$_{Rx}$ Safety Reporting**.

7.3.1 The Parties acknowledge that until [***] Isis will remain the holder of the original IND for ISIS-STAT3$_{Rx}$ (although this does not preclude AstraZeneca opening its own US IND for ISIS-STAT3$_{Rx}$ during that period) and that because AstraZeneca will conduct a Clinical Study in [***] in accordance with the STAT3 Research and Development Plan during such period, it is important that Isis and AstraZeneca coordinate their respective ISIS-STAT3$_{Rx}$ clinical trial and pre-clinical activities, including the collection and reporting of adverse events involving ISIS-STAT3$_{Rx}$. Within [***] days after the Effective Date, the Parties will develop and agree in writing on a Drug Safety Information Agreement that will include safety data delivery procedures governing the collection, investigation, reporting, and delivery of information from AstraZeneca to Isis

concerning any adverse experiences, and any product quality and product complaints involving adverse experiences related to ISIS-STAT3$_{Rx}$, sufficient to enable Isis to comply with its legal and regulatory obligations and internal processes and consistent with the terms of this Agreement. Upon transfer of Isis' ISIS-STAT3$_{Rx}$ IND to AstraZeneca and assumption by AstraZeneca of regulatory responsibilities under the IND, AstraZeneca will assume responsibility for the global safety database related to ISIS-STAT3$_{Rx}$, and will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of ISIS-STAT3$_{Rx}$ and will furnish copies of such reports to Isis. The Drug Safety Information Agreement will be revised following the closure of Isis' IND.

7.3.2 Within [***] after the Effective Date with respect to the STAT3 Program, and prior to the [***] with respect to each of the other Collaboration Programs, the Parties shall enter into a mutually agreed pharmacovigilance agreement (the "***Pharmacovigilance Agreement***"). The Parties shall comply with the provisions of such agreement. If there is any inconsistency between this Agreement and the Pharmacovigilance Agreement as it relates to Product safety, the terms of the Pharmacovigilance Agreement will prevail to the extent of such inconsistency.

ARTICLE 8.
FINANCIAL PROVISIONS

8.1. **STAT3 and [***] License Fee; Oncology Target Option Fees**. Within 30 days following the Effective Date, AstraZeneca will pay Isis an up-front fee of $25,000,000, allocated as follows:

(i) $[***] in partial consideration for the licenses granted by Isis to AstraZeneca under Section 6.1.1 for STAT3 Products;

(ii) $[***] in partial consideration for the licenses granted by Isis to AstraZeneca under Section 6.1.2 for [***] Products; and

(iii) An initial payment of $[***] in partial consideration for the Options granted by Isis to AstraZeneca under Section 3.5 for each Oncology Target.

8.2. **Oncology Target License Fees**. On an Option-by-Option basis, following AstraZeneca's written notice to Isis stating that AstraZeneca is exercising such Option in accordance with this Agreement, AstraZeneca will pay Isis a license fee of $[***] within 30 days after AstraZeneca's receipt from Isis of an invoice for such license fee (for a total of $[***] if AstraZeneca exercises all three of its Options hereunder or, a total of $[***] if a fourth Oncology Collaboration Program is added under Section 2.2.4 (for a total of four Options) and AstraZeneca exercises all four of its Options hereunder).

8.3. **Remaining Payment for the Options to the Oncology Targets**. In partial consideration for the Options granted by Isis to AstraZeneca under Section 3.5 for each Oncology Target, within [***] days following the Effective Date, AstraZeneca shall notify Isis whether it wishes to continue with the Oncology Collaboration, and if it does will pay Isis $6,000,000 within 30 days after AstraZeneca's receipt from Isis of an invoice from Isis for such amount. For the avoidance of doubt, only one payment of $6,000,000 is payable under this Section 8.3. If AstraZeneca either (i) does not notify Isis in writing within [***] days following the Effective Date that it wishes to proceed with the Oncology Collaboration, or (ii) notifies Isis in writing that AstraZeneca is not proceeding, then all of the Options will expire and the remaining payment of $6,000,000 under this Section 8.3 shall not be payable.

8.4. **Milestone Payments for Achievement of Milestone Events by a STAT3 Product**. If there is a High Response Outcome in the Phase 1/2 Trial and the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) above, then, in accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in Column 1 of TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by a STAT3 Product. If there is a Medium Response Outcome (or a Low Response Outcome) in the Phase 1/2 Trial and the license granted by Isis to AstraZeneca under Section 6.1.1 is not terminated under Section 1.2.3(f)(i) above, then, in accordance with Section 8.7.5 and subject to the terms of Section 1.2.3(h), AstraZeneca will pay to Isis the milestone payments as set forth in Column 2 of TABLE 1 below when a milestone event listed in TABLE 1 is first achieved by a STAT3 Product:

TABLE 1

STAT3 Product Milestone Event	Column 1 STAT3 Product Milestone Event Payment for High Response Outcome	Column 2 STAT3 Product Milestone Event Payment for Medium Response Outcome or Low Response Outcome
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]

8.5. **Milestone Payments for Achievement of Milestone Events by an [***] Product**. In accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 2 below when a milestone event listed in TABLE 2 is first achieved by an [***] Product:

TABLE 2

[***] Product Milestone Event	[***] Product Milestone Event Payment
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

8.6. **Milestone Payments for Achievement of Milestone Events by an Oncology Product**. On an Oncology Target-by-Oncology Target basis, in accordance with Section 8.7.5, AstraZeneca will pay to Isis the milestone payments as set forth in TABLE 3 below when

a milestone event listed in TABLE 3 is first achieved by an Oncology Product targeting such Oncology Target:

TABLE 3

Oncology Product Milestone Event	Oncology Product Milestone Event Payment
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

8.7. **Limitations on Milestone Payments; Exceptions; Notice**.

8.7.1. Each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the milestone event regardless of how many Products achieve such milestone event.

8.7.2. Each milestone payment set forth in TABLE 3 above will be paid only once per each Oncology Target upon the first achievement of the milestone event regardless of how many Products for such Oncology Target achieve such milestone event.

8.7.3. If a particular milestone event is not achieved because Development or Commercial activities transpired such that achievement of such earlier milestone event was unnecessary or did not otherwise occur, then upon

achievement of a later milestone event the milestone event payment applicable to such earlier milestone event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] milestone event, both the [***] and [***] milestone event payments are due. Similarly, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] milestone event, both the [***] and [***] milestone event payments are due.

8.7.4. In addition, if a particular milestone event is achieved contemporaneously or in connection with another milestone event, then upon achievement of one such milestone event the other milestone event will also be deemed achieved and the milestone payments for both milestone events are due. For example, if AstraZeneca achieves the [***] milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the [***] and the [***] milestone event payments are due. Similarly, if AstraZeneca achieves the [***] milestone event and the [***] ([***]) that was the subject of such milestone event [***], then both the [***] and the [***] milestone event payments are due.

8.7.5. Each time a milestone event is achieved under this ARTICLE 8, AstraZeneca will send Isis, or Isis will send AstraZeneca, as the case may be, a written notice thereof promptly (but no later than five Business Days) following the date of achievement of such milestone event. Thereafter, Isis will promptly invoice AstraZeneca for the achievement of any milestone event under this ARTICLE 8 and such milestone payment will be due within 30 days after AstraZeneca's receipt of such invoice.

8.8. Royalty Payments to Isis.

8.8.1. **AstraZeneca Full Royalty**. As partial consideration for the rights granted to AstraZeneca hereunder, subject to the provisions of this Section 8.8.1 and Section 8.8.2, AstraZeneca will pay to Isis royalties on Annual worldwide Net Sales of Products sold by AstraZeneca, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 4 below (the "***AstraZeneca Full Royalty***"):

TABLE 4

Royalty Tier	Annual Worldwide Net Sales of STAT3 Products	High Response Outcome Royalty Rate	Medium Response Outcome/Low Response Outcome Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%	[***]%

Royalty Tier	Annual Worldwide Net Sales of [***] Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Royalty Tier	Annual Worldwide Net Sales of Oncology Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Annual worldwide Net Sales will be calculated by taking the aggregate sum of Net Sales of Products for all countries worldwide.

(a) AstraZeneca will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and AstraZeneca will provide reports and payments to Isis consistent with Section 8.10. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Period.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to AstraZeneca as set forth in Section 6.3.1 will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 8.

8.8.2. **Application of Royalty Rates**. All royalties set forth under Section 8.8.1 are subject to the provisions of this Section 8.8.2, and are payable as follows:

(a) **Royalty Period**. AstraZeneca's obligation to pay Isis the AstraZeneca Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), and (iii) the [***] ([***]) anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Royalty Period***").

(b) **Limitation on Aggregate Reduction for AstraZeneca Royalties**. In no event will the aggregate royalty offsets under Section 8.9.2(a)(i) and Section 8.9.4(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of [***].

(c) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], AstraZeneca's obligation to make royalty payments hereunder in such country will end on the expiration of the Royalty Period in such country.

8.9. Third Party Payment Obligations.

8.9.1. Existing In-License Agreements.

(a) ***Isis' Existing In-License Agreements***. Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to AstraZeneca under Section 6.1.1 and Section 6.1.2 or that may be licensed to AstraZeneca under Section 6.1.3, as the case may be, are in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed in APPENDIX 6 (such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any payment obligations arising under the Isis In-License Agreements:

(i) as they apply to STAT3 Products or [***] Products, will be paid by [***] as [***], and

(ii) as they apply to Isis Product Specific Patents licensed in connection with the applicable Oncology Product after Option exercise, will be paid by [***] as [***], and

(iii) in connection with the applicable Oncology Product as they apply to Isis Core Technology Patents and Isis Manufacturing and Analytical Know-How and Isis Manufacturing and Analytical Patents will be paid by [***] as [***].

(b) ***AstraZeneca's Existing In-License Agreements***. AstraZeneca will be solely responsible for any Third Party Obligations that become payable by AstraZeneca to Third Parties under any agreements or arrangements AstraZeneca has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by AstraZeneca, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs under this Agreement.

8.9.2. New In-Licensed Additional Product-Specific Patents.

(a) **Additional STAT3/[***] Product-Specific Patents**.

(i) AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Commercialize a STAT3 Product or [***] Product ("***Additional STAT3/[***] Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with,

and obtain a license from the Third Party Controlling such Additional STAT3/[***] Product-Specific Patents. If AstraZeneca obtains any such Additional STAT3/[***] Product-Specific Patents then, subject to Section 8.8.2(b), AstraZeneca may offset an amount equal to [***]% of any [***] paid by AstraZeneca to such Third Party with respect to such Product against any [***]. [***].

(ii) If, however, AstraZeneca elects not to obtain such a license to such Additional STAT3/[***] Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional STAT3/[***] Product-Specific Patents and will include such Additional STAT3/[***] Product-Specific Patents in the license granted to AstraZeneca under Section 6.1.1 or Section 6.1.2 (as applicable) if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to STAT3 Products or [***] Products.

(b) **Additional Oncology Collaboration Product-Specific Patents**.

(i) **Prior to Option Exercise**. If, after an Oncology Target is selected but prior to Option exercise for a particular Oncology Target, Isis obtains Third Party Patent Rights necessary to Commercialize an Oncology Product where such Patent Right would have satisfied the definition of an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, then to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license to be granted to AstraZeneca under Section 6.1.3 if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to such Oncology Products.

(ii) **After Option Exercise**.

(1) On an Oncology Target-by-Oncology Target basis, after Option exercise, AstraZeneca or Isis, as the case may be, will promptly provide the other Party written notice of any additional Third Party Patent Rights necessary to practice an Isis Product-Specific Patent to Commercialize an Oncology Product ("***Additional Oncology Product-Specific Patents***") it believes it has identified and AstraZeneca will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such

Additional Oncology Product-Specific Patents. If AstraZeneca obtains any such Additional Oncology Product-Specific Patents then any and all Third Party Obligations arising under such Third Party agreement will be paid by AstraZeneca as AstraZeneca Supported Pass-Through Costs.

(2) If, however, AstraZeneca elects not to obtain such a license to such Additional Oncology Product-Specific Patents, AstraZeneca will so notify Isis, and Isis may obtain such a license to such Additional Oncology Product-Specific Patents and will include such Additional Oncology Product-Specific Patents in the license granted to AstraZeneca under Section 6.1.3 if AstraZeneca agrees in writing to pay Isis as AstraZeneca Supported Pass-Through Costs any and all costs arising under such Third Party agreement as they apply to such Oncology Products.

8.9.3. **Additional Core IP In-License Agreements**. Isis will negotiate with, and use Commercially Reasonable Efforts to obtain a license from, any Third Party controlling intellectual property that is necessary to practice an Isis Core Technology Patent to Commercialize a Product ("***Additional Core IP***"). For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) specific drug compositions, sequences, therapeutic methods, formulation or delivery technology, manufacturing or analytical methods, or other active ingredients. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as the case may be), and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

8.9.4. **Disputes Regarding Additional STAT3/[***] Product-Specific Patents and Additional Core IP**.

(a) If Isis does not agree that certain intellectual property identified by AstraZeneca pursuant to Section 8.9.2(a) is an Additional STAT3/[***] Product-Specific Patent, or if AstraZeneca does not agree that a license is not necessary to practice an Isis Core Technology Patent to Commercialize a Product as provided in Section 8.9.3, Isis or AstraZeneca, as applicable will send written notice to such effect to the other Party, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is an Additional STAT3/[***] Product-Specific Patent or whether a license is necessary to practice an Isis Core Technology Patent to Commercialize a Product. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of

determining whether [***]. The costs of any Third Party expert engaged under this Section 8.9.4 will be paid by the Party against whose position the Third Party lawyer's determination is made.

(b) Notwithstanding the determination of the Third Party lawyer under Section 8.9.4(a), if a Third Party Controlling an Additional STAT3/[***] Product-Specific Patent is awarded a judgment from a court of competent jurisdiction arising from its claim against AstraZeneca asserting that [***], AstraZeneca will be permitted to [***].

8.10. **Payments**.

8.10.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, AstraZeneca will make royalty payments to Isis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, AstraZeneca will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, AstraZeneca will provide Isis a preliminary, non-binding Product sales estimate for such Calendar Quarter.

8.10.2. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable (except as otherwise provided in Section 8.11), and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by AstraZeneca in accordance with the rates of exchange for the relevant month for converting such other currency into US Dollars used by AstraZeneca's internal accounting systems, which are independently audited on an annual basis and which are in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations.

8.10.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, AstraZeneca will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by AstraZeneca hereunder.

8.11. **Audits**. During the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, AstraZeneca will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to AstraZeneca, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of AstraZeneca, such auditor will sign a nondisclosure agreement reasonably acceptable to AstraZeneca in form and substance. Any and all records of AstraZeneca examined by such independent certified public accountant will be deemed AstraZeneca's Confidential Information. Upon completion of the audit, the accounting firm will provide both AstraZeneca and Isis with a written report disclosing whether the royalty payments made by AstraZeneca are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of AstraZeneca, it is shown that AstraZeneca's payments under this Agreement were more or less than the royalty amount which should have been paid, then the relevant Party will make all payments required to be made by paying the other Party the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 8.13; *provided, however*, that any such payment by Isis to AstraZeneca will be [***]. Isis will pay for such audit, except that if AstraZeneca is found to have underpaid Isis by more than [***] of the amount that should have been paid for the audited period, AstraZeneca will reimburse Isis the reasonable fees and expenses charged by the accounting firm for the audit.

8.12. **Taxes**.

8.12.1. **Taxes On Income**. Each Party alone will be solely responsible for paying any and all Taxes (other than withholding taxes required by Applicable Law to be paid by AstraZeneca or Isis (as the case may be) levied on account of, or measured in whole or in part by reference to, the income of such Party.

8.12.2. **Indirect Taxes** All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party shall pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

The Parties shall issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within forty-five (45) days of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

8.12.3. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so. In accordance with the procedures set forth in Section 11.3 and Section 11.4, (i) the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party, and (ii) Isis will indemnify AstraZeneca for any withholding tax incurred on Isis Supported Pass-Through Costs that arises because these costs are deemed to not be beneficially owned by Isis.

8.12.4. **Tax Cooperation**. At least 15 days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary in order for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the Applicable Laws. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 8.12.

The provisions of this Section 8.12 are to be read in conjunction with the provisions of Section 14.3 below.

8.13. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement, and any payments that are pending resolution of any dispute (including under Section 1.2.4) unless the dispute is ruled in favour of the paying Party, will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

ARTICLE 9.
INTELLECTUAL PROPERTY

9.1. **Ownership**.

9.1.1. **Isis Technology and AstraZeneca Technology**. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and AstraZeneca will own and retain all of its rights, title and interest in and to the

AstraZeneca Know-How and AstraZeneca Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement. For clarity, except as otherwise expressly provided in this Agreement, the scope of licenses granted by AstraZeneca under this Agreement shall not include AstraZeneca Background Intellectual Property.

9.1.2. **Agreement Technology**. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, or creation of any invention made solely or jointly by the Parties in connection with the performance of obligations under this Agreement. Except as otherwise expressly permitted under this Agreement, neither Party or their Affiliates or respective Sublicensees shall license or exploit the Jointly-Owned Collaboration Technology outside the scope of this Agreement without the consent of the other Party, such consent not to be unreasonably withheld.

9.1.3. **Joint Patent Committee**.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 9. A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents, AstraZeneca Product-Specific Patents and Jointly-Owned Collaboration Patents that would be and/or are licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on this Agreement or the licenses granted hereunder. In addition, the JPC will ensure that all Patent Rights claiming (i) the specific composition of matter (the exact sequence and chemistry) of the [***] Development Candidate and the other [***] Lead Compounds and/or an Oncology Development Candidate, and/or (ii) methods of using such [***] Development Candidate and such [***] Lead Compounds and/or an Oncology Development Candidate as a prophylactic, therapeutic or diagnostic, will be separated into their own patent applications separate from other subject matter to ensure any such claims are licensed to AstraZeneca under Section 6.1.2 and assigned as Assignable [***] Product-Specific Patents and/or Isis Product Specific Patents under Section 6.3.1. Isis' obligation to participate in the JPC will terminate on

the date Isis is no longer obligated to participate in the JSC. Thereafter, Isis will have the right and expects, but is not obligated, to participate in JPC meetings. In the case of existing Licensed Patents as of the Effective Date (e.g., STAT3) that are necessary or useful to exploit a STAT3 Compound/Product in the Field, the Parties are obligated to participate in JPC meetings to cooperate with respect to the activities set forth in this ARTICLE 9.

(b) In addition, the JPC will be responsible for the determination of inventorship. The determination of inventorship will be made in accordance with United States patent laws and therefore this will determine if the invention is solely or jointly owned by the relevant Party or Parties. The JPC will comprise an equal number of members from each Party, which may be one from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 9. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Senior Representatives for input and resolution pursuant to Section 14.1.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

9.2. **Prosecution and Maintenance of Patents**.

9.2.1. **Patent Filings**. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 9.2.2, Section 9.2.3 or Section 9.2.4 will endeavor to obtain patent protection for the Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

9.2.2. **Licensed Patents and AstraZeneca Patents**.

(a) **Isis Core Technology Patents and Isis Manufacturing and Analytical Patents**. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and, subject to Section 9.2.4, Licensable [***] Product-Specific Patents.

(b) **Isis Product-Specific Patents and Jointly-Owned Collaboration Patents**. On a Gene Target-by-Gene Target basis, so long as the applicable license to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) is in effect, AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of:

(i) With respect to STAT3 Products and Oncology Products licensed to AstraZeneca, the Isis Product-Specific Patents and Jointly-Owned Collaboration Patents; and

(ii) With respect to [***] Products, the Assignable [***] Product-Specific Patents,

In each case to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such license, subject to Section 9.2.3 and Section 9.2.4, and AstraZeneca will grant Isis the license set forth in Section 6.3.2.

(c) **AstraZeneca Patents**. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of all AstraZeneca Patents, subject to Section 9.2.3 and Section 9.2.5.

9.2.3. **Jointly-Owned Collaboration Patents**. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents that (i) do not Cover Products, and (ii) have not been licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that Cover Products. AstraZeneca will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Collaboration Patents licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that Cover Products.

9.2.4. **Prosecution of Licensable [***] Product-Specific Patents**.

(a) ***Prosecution Principles***. Because the license granted by Isis to AstraZeneca under Section 6.1.2 is limited in scope to the AstraZeneca [***]-Field, Isis may have an additional licensee under the Licensable [***] Product-Specific Patents to exploit Isis [***]-Field ASOs in the Isis [***]-Field (an "***Isis [***]-Field ASO Licensee***"). The purpose of this provision is to foster the full and complete development, maintenance, and protection of the Licensable [***] Product-Specific Patents and to protect the rights of all interested parties, by outlining (i) the procedures for filing, prosecuting, and maintaining the Licensable [***] Product-Specific Patents, (ii) Isis' commitment to fairly control filing, prosecution, and maintenance of the Licensable [***] Product-Specific Patents, and (iii) equitable cost-sharing allocations between AstraZeneca and the Isis [***]-Field ASO Licensee related thereto.

(b) ***Procedures for Prosecution of Licensable [***] Product-Specific Patents***. Isis will have the sole right and responsibility to obtain, prosecute, and maintain throughout the world (in such countries as are commercially appropriate) the Licensable [***] Product-Specific Patents using Commercially Reasonable Efforts with the objective of obtaining maximum claim coverage for all compounds and products (including [***] Compounds and [***] Products and their uses in the Field), with Patent Costs shared equally between the Isis [***]-Field ASO Licensee and AstraZeneca (collectively, the "***Participating Parties***"), or shared equally between AstraZeneca and Isis if no such Isis [***]-Field ASO Licensee exists. Isis, as controlling party (or its outside counsel), will provide the Participating Parties with an update of the filing, prosecution, and maintenance status for each of such Licensable [***] Product-Specific Patent on a periodic basis and will reasonably consult and cooperate with the Participating Parties with respect to the preparation, filing, prosecution, and maintenance of such Licensable [***] Product-Specific Patents, including providing the Participating Parties with drafts of proposed filings as soon as reasonably possible after such drafts are prepared and, in any case, in sufficient time to allow the Participating Parties to review and comment before such filings are due. Isis (or its outside counsel) will provide the Participating Parties with copies of any documents relating to the filing, prosecution, and maintenance of such Licensable [***] Product-Specific Patents promptly upon their being filed or received. For clarity, Isis may cease prosecuting or maintaining particular applications or patents in the Licensable [***] Product-Specific Patents in selected jurisdictions, if Isis determines that it is not commercially reasonable to continue such efforts; *provided, however*, that Isis will not discontinue such prosecution or maintenance with respect to a particular issued Licensable [***] Product-Specific Patent that Covers the [***] product, [***] Development Candidate or any other [***] Lead Compounds, or the use thereof and will not discontinue such prosecution or maintenance without first notifying AstraZeneca, and AstraZeneca will have the right, but not the obligation, to prosecute and maintain such Licensable [***] Product-Specific Patent in the applicable country at its own expense with counsel of its own choice by providing written notice to Isis within 30 days after AstraZeneca receives such discontinuance notice from Isis.

9.2.5. **Other Matters Pertaining to Prosecution and Maintenance of Patents**.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Collaboration Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 9.2.2, Section 9.2.3, Section 9.2.4 or this Section 9.2.5, including by providing copies of material data as it arises, any office actions or office action responses or

other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If AstraZeneca elects (i) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patents or Isis Product-Specific Patents that have been licensed or assigned to AstraZeneca under this Agreement or the AstraZeneca Product-Specific Patents ("***AstraZeneca-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any AstraZeneca-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the AstraZeneca-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then AstraZeneca will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such AstraZeneca-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, AstraZeneca will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such

AstraZeneca-Prosecuted Patent in such country in Isis' own name, but only to the extent that AstraZeneca is not required to take any position with respect to such abandoned AstraZeneca-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by AstraZeneca under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such AstraZeneca-Prosecuted Patent under this Section 9.2.5(b), Isis will have no obligation to notify AstraZeneca if Isis intends to abandon such AstraZeneca-Prosecuted Patent.

(c) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Jointly-Owned Collaboration Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 9.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Collaboration Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 9.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 9.2.5(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

9.3. Patent Costs.

9.3.1. Jointly-Owned Collaboration Patents. Unless the Parties agree otherwise, Isis and AstraZeneca will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Collaboration Patents.

9.3.2. Licensed Patents and AstraZeneca Patents. Except as set forth in Section 9.2.4 and Section 9.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 9.2.

9.4. Defense of Claims Brought by Third Parties.

9.4.1. Oncology Products — Prior to Option Exercise. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is

infringed by the Development, Manufacture or Commercialization of any Oncology Product being researched or developed under an Oncology Collaboration Program with respect to which AstraZeneca has not yet exercised its Option, Isis will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If Isis elects to defend against such Proceeding, then Isis will have the sole right to direct the defense and to elect whether to settle such claim; *provided, however*, Isis will not settle such Proceeding without the prior written consent of AstraZeneca (such consent not to be unreasonably withheld, conditioned or delayed). AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 9.4, and Isis will keep AstraZeneca apprised of the progress of such Proceeding. If Isis elects not to defend against such a Proceeding, then Isis will so notify AstraZeneca in writing within 60 days after Isis first receives written notice of the initiation of such Proceeding, and AstraZeneca will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter AstraZeneca will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of Isis, which consent will not be unreasonably withheld, delayed or conditioned). In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 9.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 9.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

9.4.2. STAT3 Products, [***] Products and Oncology Products After Option Exercise. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of any (i) STAT3 Product or [***] Product being developed or commercialized by AstraZeneca under a license granted under Section 6.1.1 or Section 6.1.2, or (ii) Oncology Product being developed or commercialized by AstraZeneca under a license granted under Section 6.1.3, then in any of those cases AstraZeneca will have the first right, but not the obligation, to defend against any such Proceeding at its sole cost and expense. If AstraZeneca elects to defend against such Proceeding, then AstraZeneca will have the sole right to direct the

defense and to elect whether to settle such claim (but only with the prior written consent of Isis, not to be unreasonably withheld, conditioned or delayed). Isis will reasonably assist AstraZeneca in defending such Proceeding and cooperate in any such litigation at the request and expense of AstraZeneca. AstraZeneca will provide Isis with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 9.4, and AstraZeneca will keep Isis apprised of the progress of such Proceeding. If AstraZeneca elects not to defend against a

Proceeding, then AstraZeneca will so notify Isis in writing within 60 days after AstraZeneca first receives written notice of the initiation of such Proceeding, and Isis will have the right, but not the obligation, to defend against such a Proceeding at its sole cost and expense and thereafter Isis will have the sole right to direct the defense thereof, including the right to settle such claim (but only with the prior written consent of AstraZeneca, which consent will not be unreasonably withheld, delayed or conditioned). Notwithstanding the foregoing, if [***]; *provided*, *however*, [***]. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 9.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 9.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party. Notwithstanding the foregoing, if a Proceeding described under this Section 9.4.2 involves one or more Licensable [***] Product-Specific Patents and there is an Isis [***]-Field ASO Licensee as contemplated under Section 9.2.4, then the defense against any such Proceeding will be conducted in the collective interest of, such Isis [***]-Field ASO Licensee and AstraZeneca, and this Section 9.4.2 will be read and construed in a manner that is consistent with the principles described in Section 9.2.4 except that AstraZeneca will retain sole control in respect of the defense strategy for the Assignable [***] Product-Specific Patents.

9.4.3. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. AstraZeneca will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide AstraZeneca with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 9.4.3, and Isis will promptly furnish AstraZeneca with a copy of each communication relating to the alleged infringement received by Isis.

9.4.4. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 9.4.1 and Section 9.4.3, to the extent that a Party's defense against a Third Party claim of infringement under this Section 9.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general

concepts of Section 9.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 9.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 9.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

9.5. **Enforcement of Patents Against Competitive Infringement**.

9.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a Gene Target in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 9.5.6 below, such written notice will be given within 10 days.

9.5.2. **Control of Competitive Infringement Proceedings**. For any Competitive Infringement with respect to a Product (except for a Discontinued Product) licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable) that occurs after AstraZeneca is granted such license, so long as part of such Proceeding AstraZeneca also enforces any Patent Rights Controlled by AstraZeneca (including any Isis Product-Specific Patents assigned by Isis to AstraZeneca under this Agreement) being infringed that Cover such Product, then AstraZeneca will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* AstraZeneca will have the right to control such litigation. If AstraZeneca fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if AstraZeneca has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and AstraZeneca will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, if [***]; *provided*, *however*, [***]. Notwithstanding the foregoing, if a Competitive Infringement described under this Section 9.5 involves one or more Licensable [***] Product-Specific Patents and there is an Isis [***]-Field ASO Licensee as contemplated under Section 9.2.4, then the

institution, prosecution, and control of a Proceeding with respect thereto will be conducted in the collective interest of, such Isis [***]-Field ASO Licensee and AstraZeneca, and this Section 9.5 will be read and construed in a manner that is consistent with the principles described in Section 9.2.4 except that AstraZeneca will retain sole control in respect of the defense strategy for the Assignable [***] Product-Specific Patents.

9.5.3. Joinder.

(a) If a Party initiates a Proceeding in accordance with this Section 9.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 9.5.4, the costs and expenses of each Party incurred pursuant to this Section 9.5.3(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 9.5.3, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

9.5.4. Share of Recoveries. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 9.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds will be allocated as follows: (A) if Isis initiates the Proceeding pursuant to Section 9.4.1, Section 9.4.2 or Section 9.4.3, [***]; (B) if AstraZeneca initiates the Proceeding pursuant to Section 9.4.1, AstraZeneca will receive and retain [***]% the remaining proceeds and Isis will receive and retain [***]% of the remaining proceeds; and (C) if AstraZeneca initiates the Proceeding pursuant to Section 9.4.2, [***].

9.5.5. Settlement. Notwithstanding anything to the contrary in this ARTICLE 9, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 9 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

9.5.6. 35 USC 271(e)(2) Infringement. Notwithstanding anything to the contrary in this Section 9.5, solely with respect to Licensed Patents that have not been

assigned to AstraZeneca under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 9.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

9.6. Other Infringement.

9.6.1. Jointly-Owned Collaboration Patents. With respect to the infringement in the Field of a Jointly-Owned Collaboration Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 9.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) (A) if the Parties jointly initiate a Proceeding pursuant to this Section 9.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 9.6.1, [***].

9.6.2. Patents Solely Owned by Isis. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

9.6.3. Patents Solely Owned by AstraZeneca. AstraZeneca will retain all rights to pursue an infringement of any Patent Right solely owned by AstraZeneca which is other than a Competitive Infringement and AstraZeneca will retain all recoveries with respect thereto.

9.7. Patent Listing.

9.7.1. AstraZeneca's Obligations. AstraZeneca will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product licensed to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable). Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and AstraZeneca will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, AstraZeneca will retain final decision-making authority as to the listing of all applicable Patent Rights for a Product that are not Isis Core

Technology Patents, Isis Manufacturing and Analytical Patents or Licensable [***] Product-Specific Patents, regardless of which Party owns such Patent Rights.

9.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

9.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 9, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 9 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

9.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 9 will be subject to the Third Party rights and obligations under any (i) Third Party agreements the restrictions and obligations of which AstraZeneca has agreed to under Section 8.9.2(a)(ii), Section 8.9.2(b)(i) or Section 8.9.2(b)(ii)(2), (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to AstraZeneca hereunder and, this Agreement purports to grant any such rights to AstraZeneca, Isis will act in such regard with respect to such Patent Rights at AstraZeneca's direction.

9.10. **Additional Rights and Exceptions**. Notwithstanding any provision of this ARTICLE 9, but subject to Section 9.2.4 and Section 9.4.4, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Licensable [***] Product-Specific Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

9.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, and AstraZeneca will determine which Isis Product-Specific Patents will be extended. For clarity, with respect to any Isis

Product-Specific Patent for which AstraZeneca has an exclusive license under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable), as between AstraZeneca and any Third Party granted a license by Isis outside the Field under any such Isis Product-Specific Patents, AstraZeneca will determine which Isis Product-Specific Patents will be extended.

9.12. **No Challenge**. As a material inducement for Isis entering into this Agreement, AstraZeneca covenants to Isis that during the Agreement Term, solely with respect to rights to the Licensed Patents that are included in a license granted or that may be granted to AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3 (as applicable), AstraZeneca, its Affiliates or Sublicensees will not, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents. For purposes of clarification and without limiting any other available remedies, subject to any applicable cure period provided herein for breaches of this Section 9.12 that are curable (i.e., which would allow AstraZeneca the opportunity to rescind any wrongfully brought actions by it, its Affiliates, or Sublicensees), if AstraZeneca takes any of the actions described in clause (a) or clause (b) of this Section 9.12, AstraZeneca will have materially breached this Agreement and Isis may terminate this Agreement under Section 12.2.2(b).

ARTICLE 10.
REPRESENTATIONS AND WARRANTIES

10.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants as of the Effective Date, and covenants, to the other Party that:

10.1.1. it has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and that it has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

10.1.2. this Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity;

10.1.3. all necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been

obtained;

10.1.4. the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound;

10.1.5. All employees, consultants, or (sub)contractors (except academic collaborators or Third Parties under the Permitted Licenses or Prior Agreements) of such Party or Affiliates performing development activities hereunder on behalf of such Party are, and such Party hereby covenants to the other Party that they will be, obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to such Party or Affiliate, respectively, as the sole owner thereof;

10.1.6. Such Party will, and such Party hereby covenants to the other Party that it will, perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted, and with respect to the care, handling and use in development activities hereunder of any non-human animals by or on behalf of such Party, will at all times comply (and will ensure compliance by any of its subcontractors) with all applicable national, federal, state and local laws, regulations and ordinances in performing its obligations under this Agreement; and

10.1.7. Such Party is not debarred under the United States Federal Food, Drug and Cosmetic Act or comparable Applicable Laws and it does not, and will not during the Agreement Term, employ or use the services of any person or entity who is debarred, in connection with the development, manufacture or commercialization of the Compounds or Products. If either Party becomes aware of the debarment or threatened debarment of any person or entity providing services to such Party, including the Party itself and its Affiliates or Sublicensees, which directly or indirectly relate to activities under this Agreement, the other Party will be immediately notified in writing.

10.2. **Representations, Warranties and Covenants of Isis**. Isis hereby represents and warrants to AstraZeneca, as of the Effective Date, that:

10.2.1. Isis is the owner of, or otherwise has the right to grant all rights and licenses it purports to grant to AstraZeneca with respect to the Licensed Technology

under this Agreement for Compounds identified by Isis on or before the Effective Date or Oncology Collaboration Programs as they exist on the Effective Date;

10.2.2. To Isis' Knowledge, all Licensed Patents that are owned by Isis ("***Isis Owned Patents***") have been filed and maintained properly and correctly in all material respects.

10.2.3. Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, transferred, licensed, conveyed or otherwise encumbered its right, title or interest in or to, the Licensed Technology (including by granting any covenant not to sue with respect thereto) in such a way as to make the representation set forth in Section 10.2.1 not true, and it will not enter into any such agreements or grant any such right, title or interest to any Person that is inconsistent with the rights and licenses granted to AstraZeneca under this Agreement;

10.2.4. To Isis' Knowledge, each of the Isis Owned Patents properly identifies each and every inventor of the claims thereof as determined in accordance with the laws of the jurisdiction in which such Patent Right is issued or such application is pending;

10.2.5. Isis has not received any written claim alleging that any of the Isis Owned Patents are invalid or unenforceable, including any Isis Owned Patents required in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date, in each case with respect to the Compounds and Products identified by Isis on or before the Effective Date;

10.2.6. Isis has not received any written claim alleging that any of Isis' activities relating to the Compounds and Products identified by Isis on or before the Effective Date infringe any intellectual property rights of a Third Party;

10.2.7. To Isis' Knowledge, (i) the licenses granted to Isis under the Isis In-License Agreements are in full force and effect, (ii) Isis has not received any written notice, and is not aware, of any breach by any party to the Isis In-License Agreements, and (iii) Isis' performance of its obligations under this Agreement (including the Collaboration Plans as they exist on the Effective Date) will not constitute a breach of Isis' obligations under the Isis In-License Agreements and the licenses granted to Isis thereunder;

10.2.8. To Isis' Knowledge, Isis does not require any additional licenses or other intellectual property rights in order for Isis to conduct its obligations under the Collaboration Plans as they exist on the Effective Date, in each case with respect to the Compounds identified by Isis on or before the Effective Date;

10.2.9. To Isis' Knowledge, in respect of the pending United States patent applications included in the Isis Owned Patents, Isis has submitted all material prior art of

which it is aware in accordance with the requirements of the United States Patent and Trademark Office;

10.2.10. To Isis' Knowledge, neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date that would be necessary or useful in order for AstraZeneca to further Develop or Commercialize Compounds contemplated under the Collaboration Plans as they exist on the Effective Date;

10.2.11. APPENDIX 10 (Prior Agreements) is a complete and accurate list of all agreements between Isis and Third Parties as of the Effective Date with respect to the Gene Targets included in this Agreement as of the Effective Date, that create material Third Party Obligations that affect the rights granted by Isis to AstraZeneca under this Agreement. The Prior Agreements have not been materially amended or extended since first being placed in the Isis data room to which AstraZeneca was given access during the negotiation of this Agreement and subject to redactions represent a true and complete and accurate copy thereof, and any such redactions are of information not necessary to disclose to understand the implications of such Prior Agreements to this Agreement; and

10.2.12. Isis has conducted, and has required its contractors and consultants to conduct, any and all preclinical and clinical studies related to the Compounds and Products in compliance with good laboratory and clinical practices and cGMP and Applicable Law, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities were conducted.

10.2.13. Isis has made available to AstraZeneca all material Regulatory Documentation for ISIS-STAT3$_{Rx}$. Isis has prepared, maintained and retained such Regulatory Documentation required to be maintained or reported pursuant to and in accordance with Applicable Law and such Regulatory Documentation does not contain any materially false or misleading statements.

10.3. **Representations, Warranties and Covenants of AstraZeneca**. AstraZeneca hereby represents and warrants to Isis that as of the Effective Date, except as explicitly disclosed in writing by AstraZeneca to Isis there are no Patent Rights comprised in AstraZeneca Background IP related to STAT3 or [***] with respect to which AstraZeneca does not have the ability to grant a license or sublicense hereunder to Isis without violating the terms of any agreement with any Third Party.

10.4. **DISCLAIMER OF WARRANTY. EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 10, ASTRAZENECA AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ASTRAZENECA AND ISIS EACH SPECIFICALLY DISCLAIM ANY WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF**

QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENT RIGHTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 11.
INDEMNIFICATION; INSURANCE

11.1. **Indemnification by AstraZeneca**. AstraZeneca agrees to defend Isis, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***Isis Indemnitees***"), and will indemnify and hold harmless the Isis Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorneys' fees and other legal expenses with respect thereto (collectively, "***Losses***") arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, "***Third Party Claims***") brought against any Isis Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an AstraZeneca employee, consultant or (sub)contractor in the performance of the AstraZeneca Conducted Activities, (b) the Development or Commercialization of any Compound or Product by AstraZeneca or its Affiliates, Sublicensees or contractors, (c) any breach by AstraZeneca of any of its representations, warranties or covenants pursuant to this Agreement, or (d) the negligence or willful misconduct of AstraZeneca or any AstraZeneca Affiliate or Sublicensee in the performance of this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any Isis Indemnitee, (ii) any breach by Isis of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any Isis Indemnitee.

11.2. **Indemnification by Isis**. Isis agrees to defend AstraZeneca, its Affiliates and their respective directors, officers, stockholders, employees and agents, and their respective successors, heirs and assigns (collectively, the "***AstraZeneca Indemnitees***"), and will indemnify and hold harmless the AstraZeneca Indemnitees, from and against any Losses arising out of Third Party Claims brought against any AstraZeneca Indemnitee and resulting from or occurring as a result of: (a) any activities conducted by an Isis employee, consultant or (sub)contractor in the performance of the Isis Conducted Activities; (b) any breach by Isis of any of its representations, warranties or covenants pursuant to this Agreement, (c) the negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of Isis in the performance of this Agreement, or (d) the Development or Commercialization of any Discontinued Product by Isis or its Affiliates, Sublicensees or contractors; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any AstraZeneca Indemnitee, (ii) any breach by AstraZeneca of any of its representations, warranties, covenants or obligations pursuant to this Agreement, or (iii) any breach of Applicable Law by any AstraZeneca Indemnitee.

11.3. **Notice of Claim**. All indemnification claims provided for in Section 11.1 and Section 11.2 will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 11.1 or Section 11.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

11.4. Defense, Settlement, Cooperation and Expenses.

11.4.1. Control of Defense. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within 30 days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 11.4.1, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

11.4.2. Right to Participate in Defense. Without limiting Section 11.4.1, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided, however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 11.4.1 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under

Applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

11.4.3. Settlement. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 11.4.1, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld.

11.4.4. Cooperation. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include access during normal business hours afforded to indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable out-of-pocket costs and expenses in connection therewith.

11.4.5. Costs and Expenses. Except as provided above in this Section 11.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

11.5. Insurance.

11.5.1. Isis' Insurance Obligations. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Isis will furnish to AstraZeneca evidence of any insurance required under this Section 11.5.1, upon request.

11.5.2. AstraZeneca's Insurance Obligations. AstraZeneca hereby represents and warrants to Isis that it will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by AstraZeneca under this Agreement. AstraZeneca will maintain such self insurance throughout the Agreement Term and for five years thereafter, and will furnish to Isis evidence of such insurance, upon request.

11.6. LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 11 OR SECTION 12.3.2(i), (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT, (c) A PARTY'S BREACH OF ARTICLE 5, OR A BREACH OF SECTION 12.3.1(a) BY ASTRAZENECA OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN

ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.

11.7. Anti-Bribery and Corruption Compliance.

11.7.1 Each Party agrees, on behalf of itself, its officers, directors and employees and on behalf of its Affiliates, agents, representatives, consultants and subcontractors hired for activities undertaken for or in connection with the performance of this Agreement (together with such Party, the "***Party Representatives***") that for the performance of its obligations hereunder:

Party Representatives shall not directly or indirectly pay, offer or promise to pay, or authorize the payment of any money, or give, offer or promise to give, or authorize the giving of anything else of value, to:

(1) any Government Official in order to influence official action;

(2) any Person (whether or not a Government Official) (i) to influence such Person to act in breach of a duty of good faith, impartiality or trust ("acting improperly"), (ii) to reward such Person for acting improperly, or (iii) where such Person would be acting improperly by receiving the money or other thing of value;

(3) any other Person while knowing or having reason to know that all or any portion of the money or other thing of value will be paid, offered, promised or given to, or will otherwise benefit, a Government Official in order to influence official action for or against either Party in connection with the matters that are the subject of this Agreement; or

(4) any Person to reward that Person for acting improperly or to induce that Person to act improperly.

11.7.2 Party Representatives shall not, directly or indirectly, solicit, receive or agree to accept any payment of money or anything else of value in violation of the Anti-Corruption Laws.

11.7.3 Each Party acknowledges that its undertakings given in Sections 11.7.1 and 11.7.2 are material to the other Party in entering into a relationship with such Party.

11.7.4 Each Party, on behalf of itself and its Party Representatives, represents and warrants to the other Party that for the term of this Agreement and six years thereafter, it shall and shall procure that its Party Representatives keep and maintain accurate books and reasonably detailed records in connection with the performance of its obligation under this Agreement including all records required to establish compliance with Sections 11.7.1 and 11.7.2 above.

11.7.5 Each Party shall promptly provide the other Party with written notice of the following events: (A) upon becoming aware of any breach or violation by it or its Party Representatives of any representation, warranty or undertaking set forth in Sections 11.7.1 and 11.7.2; and (B) upon receiving a formal notification that it is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation or upon receipt of information from any of its Party Representatives connected with this Agreement that any of them is the target of a formal investigation by a Relevant Authority for a Material Anti-Corruption Law Violation.

11.7.6 For the term of this Agreement and six years thereafter, each Party shall for the purpose of auditing and monitoring the performance of its compliance with the Agreement and particularly this Section 11.7 permit the other Party, its Affiliates, any auditors of any of them and any Regulatory Authority to have access to any premises of such Party or its Party Representatives used in connection with this Agreement, together with a right to access personnel and records that relate to this Agreement ("***Audit***").

11.8 Each Party shall be responsible for any breach of any representation, warranty or undertaking in this Section 11.7 or of the Anti-Corruption Laws by any of its Party Representatives.

11.9 Each Party may disclose the terms of this Agreement or any action taken under this Section 11.7 to prevent a potential violation or continuing violation of applicable Anti-Corruption Laws, including the identity of the other Party and the payment terms, to any governmental authority if such Party determines, upon advice of counsel, that such disclosure is necessary.

ARTICLE 12.
TERM; TERMINATION

12.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 12, will continue in full force and effect until this Agreement expires as follows:

12.1.1. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to such Product (or such Discontinued Product) in such country; and

12.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Product (or last Discontinued Product) in all countries pursuant to Section 12.1.1.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 12.1 is the "***Agreement Term***."

12.2. **Termination of the Agreement**.

12.2.1. **AstraZeneca's Termination for Convenience or Change of Control**.

(a) **Termination for Convenience**. At any time following payment by AstraZeneca of the upfront fee under Section 8.1, subject to Section 12.3.1 below, AstraZeneca will be entitled to terminate this Agreement in part with respect to STAT3 Products or [***] Products for convenience by providing 90 days written notice to Isis of such termination. In addition, at any time following payment by AstraZeneca of the upfront fee under Section 8.1 and the payment under Section 8.3, subject to Section 12.3.1 below, AstraZeneca will be entitled to terminate this Agreement in its entirety or in part on a Product-by-Product, Gene Target-by-Gene Target basis for convenience by providing 90 days written notice to Isis of such termination.

(b) **Change of Control Event**. Prior to the Option Deadline for an Oncology Target or until Isis has completed the Isis Conducted Activities with respect to the STAT3 Program or [***] Program under the R&D Research and Development Plan, AstraZeneca will have the right to terminate this Agreement in whole or in part with respect to one or more Oncology Targets for which AstraZeneca has not exercised its Option or with respect to a Licensed Target, immediately upon written notice to Isis provided at any time within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event (and Isis shall be obliged to give notice on such closing, and in the event it fails to do so, AstraZeneca's right to terminate may be exercised within 90 Business Days of such closing coming to AstraZeneca's Knowledge), if such closing occurs during the Oncology Collaboration Term or before Isis has completed the Isis Conducted Activities with respect to the STAT3 Program or [***] Program under the R&D Research and Development Plan (as applicable). If at AstraZeneca's discretion, AstraZeneca decides not to terminate this Agreement with respect to a particular Gene Target pursuant to this Section 12.2.1(b) following the closing of a Change of Control Event during the Oncology Collaboration Term, then, subject to the below provisions in this Section 12.2.1, Isis' and AstraZeneca's obligations under ARTICLE 3 to perform the relevant Collaboration Program on such Gene Target will remain and Isis (or its successor) will use commercially reasonable efforts to perform the Oncology Collaboration Program on such Oncology Target in accordance with ARTICLE 3 while, to the extent reasonably practicable, maintaining confidentiality of AstraZeneca's Confidential Information from any entity acquiring Isis as a result of the Change of Control Event. As soon as reasonably possible after the public announcement of such a Change of

Control Event, Isis (or its successor) and AstraZeneca will meet to discuss in good faith how Isis (or its successor) will continue to perform its obligations under this Agreement with respect to any Licensed Targets and Oncology Targets for which AstraZeneca has not exercised its Option so that AstraZeneca can consider whether to exercise its rights of termination under this Section 12.2.1(b). If AstraZeneca does not exercise its right of termination it shall have the right, by providing Isis with written notice within 30 Business Days following notification by Isis to AstraZeneca of the closing of a Change of Control Event, to require that Isis ceases performing any or certain activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee. AstraZeneca shall be entitled to deduct an amount equal to the [***]) from its next applicable milestone or license fee payment as applicable. Without prejudice to the foregoing, if requested by AstraZeneca such measures shall include a technology transfer pursuant to the provisions of Section 6.5 or Section 6.1.4(b), in either case without charge to AstraZeneca. Furthermore, if the surviving entity following such Change of Control Event is clinically developing or commercializing a product that is directly competing with a Product under this Agreement, then, solely with respect to the Product that is subjected to such competition, AstraZeneca will no longer be bound by the disclosure requirements of Section 4.3 hereof and may require that Isis cease to participate in the JSC.

12.2.2. **Termination for Material Breach**.

(a) **AstraZeneca's Right to Terminate**. If AstraZeneca has reason to believe that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, ARTICLE 2 or ARTICLE 3, which is governed by Section 12.2.3 below), then AstraZeneca may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, AstraZeneca may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Gene Target-by-Gene Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to Isis.

(b) **Isis' Right to Terminate**. If Isis has reason to believe that AstraZeneca is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1, which is governed by Section 12.2.3 below), then Isis may deliver notice of such material breach to AstraZeneca. If the breach is curable, AstraZeneca will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment

when due, which breach must be cured within 30 days following such notice). If AstraZeneca fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis may terminate this Agreement in its entirety if such breach relates to this Agreement in its entirety, or in relevant part on a Product-by-Product, Gene Target-by-Gene Target basis if such breach does not relate to this Agreement in its entirety, by providing written notice to AstraZeneca.

12.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2 or ARTICLE 3 (as determined in accordance with Section 14.1), AstraZeneca will notify Isis and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in ARTICLE 1, ARTICLE 2 or ARTICLE 3. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2 or ARTICLE 3, then subject to Section 12.2.4 below, AstraZeneca will have the right, at its sole discretion, to terminate this Agreement in whole or in part on a Product-by-Product, Gene Target-by-Gene Target basis.

(b) If AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1 (as determined in accordance with Section 14.1), Isis will notify AstraZeneca and, within 30 days thereafter, Isis and AstraZeneca will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to AstraZeneca's use of Commercially Reasonable Efforts in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1. Following such a meeting, if AstraZeneca fails to use Commercially Reasonable Efforts as contemplated in ARTICLE 1, ARTICLE 2, ARTICLE 3 or Section 7.1, then subject to Section 12.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement in part on a Product-by-Product, Gene Target-by-Gene Target basis.

12.2.4. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 12.2.2 or Section 12.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such 60 day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 12.2.2 or Section 12.2.3, unless and until it has been determined in accordance with Section 14.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of

such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

12.2.5. Termination for Insolvency.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") or analogous provisions of Applicable Law outside the US licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code or analogous provisions of Applicable Law outside the US. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code or analogous provisions of Applicable Law outside the US. Upon the commencement of a bankruptcy proceeding of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and all embodiments which, if not already in its possession, will be promptly delivered to the non-bankrupt Party upon written request.

12.3. Consequences of Expiration or Termination of this Agreement.

12.3.1. Consequence of Termination of this Agreement. If this Agreement is terminated by a Party in accordance with this ARTICLE 12 in its entirety or on a Product-by-Product, Gene Target-by-Gene Target basis (including under Section 1.2.3, Section 2.2.3 or Section 2.2.4(b)) at any time and for any reason, the following terms will apply to any such termination, but only to the extent of any such termination (i.e., in part or in its entirety):

(a) **Licenses**. The licenses granted by Isis to AstraZeneca under this Agreement will terminate and AstraZeneca, its Affiliates, Sublicensees and Distributors will cease selling Products; *provided, that* AstraZeneca, its Affiliates, Sublicensees and Distributors shall have the right to sell any

remaining inventory of Product over a period of no greater than six months after the effective date of such termination, and AstraZeneca will pay Isis royalties in accordance with Section 8.8 on the Net Sales of such inventory of such Products, to the extent not already paid.

(b) **Option**. AstraZeneca's Option will terminate with respect to any terminated Oncology Target.

(c) **Exclusivity**. Neither Party will have any further obligations under Section 5.1 of this Agreement insofar as it relates to such termination.

(d) **Collaboration Plans**. Neither Party will have any further obligations with respect to the terminated Collaboration Plan(s).

(e) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(f) **Accrued Rights**. Termination of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination of this Agreement. For purposes of clarification, milestone payments under ARTICLE 8 accrue as of the date the applicable milestone event is achieved even if the payment is not due at that time.

(g) **Survival**. The following provisions of this Agreement will survive the expiration or earlier termination of this Agreement: Section 3.4 (Expiration of Oncology Collaboration Term) (but only with respect to the licenses and other rights granted by AstraZeneca to Isis therein), Section 3.5.2 (Options) (but only until any initiated but uncompleted IND-Enabling Toxicology Studies are completed), Section 6.1.4(d) (Effect of Termination on Sublicenses), Section 6.1.5 (Consequence of Natural Expiration of this Agreement), Section 6.3.2 (Grant-Back to Isis of Isis Product-Specific Patents), Section 8.10.3 (Record Retention), Section 8.11 (Audits), Section 8.12.3 (Withholding Tax) (but only with respect to any indemnification obligations therein), Section 9.1.1 (Isis Technology and AstraZeneca Technology), Section 9.1.2 (Agreement Technology), Section 12.2.5 (Termination for Insolvency), Section 12.3 (Consequences of Termination of this Agreement), ARTICLE 11 (Indemnification) (but excluding Section 11.7 through Section 11.9), ARTICLE 13 (Confidentiality), ARTICLE 14 (Miscellaneous) and APPENDIX 1

(Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

12.3.2. **Isis: Special Consequences of Certain Terminations**. If (A) this Agreement is terminated under Section 1.2.3, Section 2.2.3 or Section 2.2.4(b) with respect to STAT3 or [***] (as applicable), (B) AstraZeneca terminates the Agreement under Section 12.2.1 or (C) Isis terminates this Agreement under Section 12.2.2(b), Section 12.2.3(b) or Section 12.2.5, then, in addition to the terms set forth in Section 12.3.1, the following additional terms will also apply:

(i) AstraZeneca will and hereby does grant to Isis:

(1) a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all AstraZeneca Technology (excluding AstraZeneca Background IP) Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product; and

(2) a sublicensable, worldwide, non-exclusive license or sublicense, as the case may be, under all AstraZeneca Background IP Controlled by AstraZeneca as of the date of such reversion that Covers the Discontinued Product;

in each case solely to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product in the Field (such licenses will be sublicensable by Isis in accordance with Section 6.1.4, *mutatis mutandis*); and *provided that* Isis shall, in accordance with ARTICLE 11, indemnify and hold harmless AstraZeneca and its Affiliates and Sublicensees from any Losses with respect to the Development and Commercialization of such Discontinued Product under such licenses.

(ii) AstraZeneca will assign back to Isis any Patent Rights that relate to the Discontinued Product previously assigned by Isis to AstraZeneca under this Agreement;

(iii) AstraZeneca will transfer to Isis for use with respect to the Development and Commercialization of the Discontinued Product, any Know-How, data, results, regulatory information, filings, and files in the possession of AstraZeneca, or copies thereof, as of the date of such termination or reversion that relate solely to such Discontinued Product, and any other information or material specified in Section 6.5;

(iv) AstraZeneca will grant to Isis a non-exclusive, royalty-free, fully paid up license under any trademarks that are specific to

a Discontinued Product solely for use with such Discontinued Product; *provided, however*, that in no event will AstraZeneca have any obligation to license to Isis any trademarks used by AstraZeneca both in connection with the Product and in connection with the sale of any other product or service, including any AstraZeneca- or AstraZeneca-formative marks;

(v) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, and AstraZeneca will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in AstraZeneca's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents only in respect of the Discontinued Product;

(vi) upon Isis' written request pursuant to a mutually agreed supply agreement, AstraZeneca will sell to Isis any bulk API and finished Product in AstraZeneca's possession related to the Compounds that are the subject of the termination at the time of such termination, at a price equal to AstraZeneca's cost at the time such material was produced;

(vii) If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which AstraZeneca has paid Isis the license fee under Section 8.1(i), Section 8.1(ii) or Section 8.2 (as applicable), then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay AstraZeneca a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product until [***]; and

(viii) If there are any licensed rights granted by AstraZeneca to Isis under Section 12.3.2(i)(2), the Parties shall negotiate in good faith regarding a reasonable royalty for such Discontinued Product (not to exceed [***]% of Annual worldwide Net Sales of such Discontinued Product) to be paid by Isis to AstraZeneca for Discontinued Products covered by such licensed rights, with such royalty payments beginning on the date [***] and ending on the earlier of [***].

12.3.3. AstraZeneca: Special Consequences of Certain Terminations.

(a) If AstraZeneca terminates this Agreement under Section 12.2.2(a), Section 12.2.3(a) or Section 12.2.5, all of the provisions of Section 12.3.1 shall apply, *except that* AstraZeneca, its Affiliates, Sublicensees and

Distributors shall have the right to sell any remaining inventory of Product, and AstraZeneca will pay Isis royalties in accordance with Section 8.8 on the Net Sales of such inventory of such Products to the extent not already paid.

(b) If AstraZeneca has the right to terminate this Agreement under Section 12.2.2(a), Section 12.2.3(a) or Section 12.2.5, but elects to continue the Agreement, the following provisions which shall be effective upon AstraZeneca's notice of such election, shall apply:

(i) AstraZeneca may require that Isis ceases performing any activities and co-operate and take such measures as may be requested to ensure a prompt and smooth transition of such activities to AstraZeneca or its designee; and may require that Isis cease to participate in the JSC. Without prejudice to the foregoing, if requested by AstraZeneca such measures shall include a technology transfer pursuant to the provisions of Section 6.5 or Section 6.1.4(c), in either case without charge to AstraZeneca; and

(ii) any money damages that may be awarded to AstraZeneca arising from the circumstances which gave rise to the right to terminate, and any costs (the amount of such costs as mutually agreed in good faith by the Parties) incurred by AstraZeneca in connection with the transition of Isis' responsibilities under this Agreement to AstraZeneca or its designee may be setoff against any monies owed by AstraZeneca to Isis as provided in Section 14.2.2.

(c) The provisions of this Section 12.3.3 will not preclude any Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice any Party's right to obtain performance of any obligation.

ARTICLE 13.
CONFIDENTIALITY

13.1. Confidentiality; Exceptions. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Confidential Information disclosed by the other Party or its Affiliates (the "***Disclosing Party***").

13.2. Prior Confidentiality Agreement. The Mutual Confidential Disclosure Agreement executed by Isis and AstraZeneca on April 11, 2011 (including any and all amendments thereto) (the "***CDA***") will govern disclosures of Confidential Information (as defined in the CDA) between the Parties prior to the Effective Date. All Confidential Information exchanged between the Parties on or after the Effective Date under this Agreement will be subject to the terms of this ARTICLE 13.

13.3. Authorized Disclosure. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided*, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 13.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided*, *however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a

Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; (v) subject to the terms of any protective order the Disclosing Party is using to protect its own Confidential Information, to prosecute or defend litigation as permitted by this Agreement, or (vi) as mutually agreed to in writing by the Parties.

13.4. Press Release; Publications; Disclosure of Agreement.

13.4.1. Public Announcements – Generally. Upon execution of this Agreement, the Parties will issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 13.4, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

13.4.2. Use of Name. Except as set forth in Section 13.4.8, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

13.4.3. Notice of Significant Events. Each Party will immediately notify (and provide as much advance notice as possible, but at a minimum three Business Days advance notice to) the other of any significant event related to a Product (including any data or regulatory advice or approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 13.4.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least three Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

13.4.4. Disclosure of Information Related to Products. The Party that has primary control of a Product (i.e., Isis, with respect to Products for which AstraZeneca has not exercised its Option; and AstraZeneca, with respect to STAT3 Products, [***] Products and Products for which AstraZeneca has exercised its Option) has the sole right, consistent with its practice with its other products, to issue press releases or other similar public communications to disclose the progress and results regarding such Product to the public in order to satisfy its disclosure obligations under Applicable Law or to remain consistent with its normal public disclosure practices (but for clarity, in connection with the Oncology Collaboration, such disclosure would not involve disclosing a Reserved Target or an Oncology Lead Candidate until such target had become a Development Candidate) ; *provided, that* any proposed press release or other similar public communication by such controlling Party disclosing regulatory discussions, the efficacy or safety data or results related to the Product or such controlling Party's sales projections, (i) such controlling Party will submit such proposed communication to the non-controlling Party for review at least two Business Days in advance of such proposed public disclosure, (ii) the non-controlling Party will have the right to review and recommend changes to such communication, and (iii) the controlling Party will in good faith consider any changes that are timely recommended by the non-controlling Party. In addition, if at any time during such two Business Day review period, the other Party informs such Party that its proposed public disclosure discloses inventions made by either Party in the course of the research or development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (x) delay such proposed publication for a period of time reasonably necessary to permit the timely preparation and first filing of patent application(s) on the information involved, or (y) to the extent permitted by Applicable Law, remove the identified information prior to disclosure. While the Parties acknowledge that it may be

interpreted that there is overlap between this Section 13.4.4 and Section 13.4.5, for clarity, the Parties intend for this Section 13.4.4 to address public disclosures that are not primarily of a scientific or scholarly nature (which are meant to be disclosed in accordance with Section 13.4.5 below) but rather this Section 13.4.4 is designed to address more urgent disclosures required under Applicable Law or to provide investors with material information regarding Products or this Agreement in a timely manner so that they may make informed investment decisions in Isis' or AstraZeneca's stock.

13.4.5. Scientific or Clinical Presentations. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Isis or AstraZeneca for a Product, the Parties acknowledge that scientific lead time is a key element of the value of a Product under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the research or development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results, for example, without limitation, intellectual property protection, competitive intelligence, prejudicing the optimal presentation at major meetings. For clarity, in connection with the Oncology Collaboration, such disclosure would not involve disclosing a Reserved Target or an Oncology Lead Candidate until such target had become a Development Candidate unless agreed otherwise by the Parties. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 30 days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration Plans. If, during such 30 day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 30 day period, the other Party informs such Party that its proposed

publication discloses inventions made by either Party in the course of the research or development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

13.4.6. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

13.4.7. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

13.4.8. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or the Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: ISIS; NYE: AZN). Isis may include the Product (and identify AstraZeneca as its partner for the Product) in Isis' drug pipeline.

ARTICLE 14.
MISCELLANEOUS

14.1. **Dispute Resolution**.

14.1.1. **Resolution by Senior Representatives**. The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. For clarity, any decision within the JSC's decision-making authority will be finally decided by the JSC. Any dispute between the Parties which is outside the JSC's decision-making authority will be promptly presented to the Senior Vice President, Research of AstraZeneca and the Chief Operating Officer of Isis (the "***Senior Representatives***"), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim. Any dispute within the JSC's decision-making authority will not be subject to arbitration.

14.1.2. **Request for Arbitration**. If after negotiating in good faith pursuant to Section 14.1.1, the Parties fail after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within 90 days, then either Party may upon written notice to the other submit to binding arbitration pursuant to Section 14.1.3 below. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

14.1.3. **Arbitration**.

(a) Subject to Section 14.2, any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Section 14.1.1 will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 14.1.3. The arbitration will be held in New York, New York, USA according to Rules of Arbitration of the International Chamber of Commerce ("***ICC***"). The arbitration will be conducted by a panel of three arbitrators with significant experience in the pharmaceutical industry, unless otherwise agreed by the Parties, appointed in accordance with applicable ICC rules. Any arbitration herewith will be conducted in the English language to the maximum extent possible. The arbitrators will render a written decision no later than six months following the selection of the arbitrators, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in U.S. dollars free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 14.1.3. With respect to money damages, nothing contained herein will be construed to permit the arbitrator or any court or any other forum to award punitive or exemplary damages, except in the case of breach of ARTICLE 13. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages, except in the case of breach of ARTICLE 13. Each Party will pay its legal fees and costs related to the arbitration (including witness and expert fees). Judgment on the award so rendered will be final and may be entered in any court having jurisdiction thereof.

(b) EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER.

14.1.4. **Court Actions**. Nothing contained in this Agreement will deny either Party the right to seek injunctive or other equitable relief from a court of competent jurisdiction in the context of a *bona fide* emergency or prospective irreparable harm, and such an action may be filed and maintained notwithstanding any ongoing dispute resolution discussions or arbitration proceeding. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 14.1.3.

14.2. **Governing Law; Jurisdiction; Equitable Relief, Losses**.

14.2.1. This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA, without reference to any rules of

conflicts of laws. For clarification, any dispute relating to the scope, validity, enforceability or infringement of any Patents will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

14.2.2. Each Party acknowledges and agrees that the restrictions set forth in Section 5.1 of this Agreement are reasonable and necessary to protect the legitimate interests of the other Party and that the other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any of these provisions will probably result in irreparable injury to the other Party for which there will be no adequate remedy at law. In the event of a breach or threatened breach of any such provision, each Party will be authorized and entitled to obtain from any court of competent jurisdiction equitable relief, whether preliminary or permanent, specific performance and an equitable accounting of all earnings, profits and other benefits arising from such breach, which rights will be cumulative and in addition to any other rights or remedies to which such Party may be entitled in law or equity. Each Party agrees to waive any requirement that the other Party (a) post a bond or other security as a condition for obtaining any such relief, and (b) show irreparable harm, balancing of harms, consideration of the public interest or inadequacy of monetary damages as a remedy. Nothing in this Section 14.2.2 is intended, or should be construed, to limit a Party's rights to equitable relief or any other remedy for a breach of any other provision of this Agreement. Except for (i) the offsets and credits explicitly set forth in Section 8.9.2(a), Section 8.9.4(b) and Section 8.11, (ii) any amount awarded to be paid by one Party to the other by the panel of arbitrators in a final and binding arbitration proceeding adjudicated under Section 14.1.3, and (iii) any offset of undisputed but unpaid amounts under this Agreement, neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

14.2.3. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 11.1 or Section 11.2, and the offsets under Section 8.9.4(b)).

14.3. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if a Party transfers or assigns this Agreement to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"),

will [***] due that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 8 for the [***] such that the Non-Transferring Party receives [***]. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without AstraZeneca's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction; *provided, however*, that Isis will provide AstraZeneca advance notice of any such proposed payment factoring transaction giving AstraZeneca a reasonable opportunity to provides comments (which Isis will consider in good faith); [***]. Any purported assignment or transfer made in contravention of this Section 14.3 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] the Transferring Party [***]. To assist the Transferring Party in determining when a [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the Transferring Party [***] payment under this Section 14.3, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party [***] or [***]), the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party s' Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

14.4. **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

14.5. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Isis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to AstraZeneca, addressed to:	AstraZeneca AB SE-431 83 Molndal Sweden Attention: Legal Department Fax: +46 31 7763871
with a copy to:	AstraZeneca UK Limited Strategic Planning and Business Development Alderley House Alderley Park Macclesfield Chehsire SK10 4TF Fax: +44 1625 518805

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service. It is understood and agreed that this Section is not intended to govern the day to day business communications necessary between the parties in performing their duties, in due course, under the terms of this Agreement.

14.6. **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

14.7. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a

waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

14.8. **Severability**. If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

14.9. **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and Schedules) sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof, and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

14.10. **Relationship of the Parties**. It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

14.11. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word “including” (in its various forms) means “including without limitation,” (c) the words “will” and “shall” have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) references to a particular Person include such Person’s successors and assigns to the extent not prohibited by this Agreement, (f) unless otherwise specified, “$” is in reference to United States dollars, and (g) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

14.12. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards, consistently applied.

14.13. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

14.14. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

14.15. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

14.16. **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

14.17. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ASTRAZENECA AB

By: */s/ Jan-Olof Jacke*
Name: Jan-Olof Jacke
Title: CFO AstraZeneca AB

SIGNATURE PAGE TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: Chief Operating Officer

SIGNATURE PAGE TO COLLABORATION, LICENSE AND DEVELOPMENT AGREEMENT

List of Appendices and Schedules

APPENDIX 1 — Definitions

APPENDIX 2 —STAT3 Research and Development Plan and [***] Research and Development Plan

APPENDIX 3 — Oncology Research and Development Plans

APPENDIX 4 — Isis' Lead Candidate Checklist

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"$" means the lawful currency of the United States.

"***Acceptance of Filing***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance of Filing will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by AstraZeneca, its Affiliate or Sublicensee of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Additional Core IP***" has the meaning set forth in Section 8.9.3.

"***Additional Plan Costs***" means [***].

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 12.1.

"***Alliance Manager"*** has the meaning set forth in Section 4.2.

"***Annual***" or "***Annually***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"Anti-Corruption Laws" means the U.S. Foreign Corrupt Practices Act, as amended, the UK Bribery Act 2010, as amended, and any other applicable anti-corruption laws and laws for the prevention of fraud, racketeering, money laundering or terrorism.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including

any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means (i) with respect to a Product in the EU, the earlier to occur of (A) approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product, including pricing approval, in such jurisdiction in accordance with Applicable Laws, or (B) the first commercial sale of a Product in the EU; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"[***]" means [***].

"[***] ***Research and Development Plan***" means the research and development plan for the [***] Program (initially as attached hereto as Appendix 2) as amended from time to time in accordance with this Agreement.

"[***] ***Compound***" means any ASO that is designed to bind to the RNA that encodes [***], where such ASO is (i) discovered or Controlled by Isis prior to the Effective Date, or (ii) discovered by Isis in the performance of the [***] Research and Development Plan.

"[***] ***Development Candidate***" means the [***] Compound selected by AstraZeneca as a Development Candidate.

"[***] ***Development Candidate Decision Deadline***" has the meaning set forth in Section 2.2.3.

"[***] ***Lead Candidate***" means the Lead Candidate designated by Isis as a potential [***] Development Candidate.

"[***] ***Lead Compound***" has the meaning set forth in Section 5.1.3. The [***] Lead Compound sequences will be set forth in the minutes of the JSC.

"[***] ***Product***" means a finished product containing an [***] Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"[***] ***Program***" means the research and development program for [***] Products under this Agreement.

"***ASO***" means a single-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***Assignable*** [***] ***Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date *claiming*: (i) the specific composition of matter (the exact sequence and chemistry) of the [***] Development Candidate and the other [***] Lead Compounds (or any [***] Product incorporating such [***] Development Candidate or other [***] Lead Compounds), and/or (ii) methods of using such [***] Development Candidate and such other [***] Lead Compounds (or any [***] Product incorporating such [***] Development Candidate or other [***] Lead Compounds) as a prophylactic, therapeutic or diagnostic.

"***AstraZeneca***" has the meaning set forth in the Preamble of this Agreement.

"***AstraZeneca*** [***]-***Field***" has the meaning set forth in Section 5.1.3(a)(i).

"***AstraZeneca Background Intellectual Property***" means any Know-How and Patent Rights that: (i) were Controlled by AstraZeneca prior to the Effective Date; and/or (ii) are Controlled by AstraZeneca on or after the Effective Date that were not created or acquired in connection with performance of any Collaboration Plan and/or in connection with the exploitation of a Compound or Product, which Patents and Know-How is necessary to Develop, register, Manufacture or Commercialize a Product in the Field.

"***AstraZeneca Conducted Activities***" means, under a Collaboration Plan, any and all research, pre-clinical and/or clinical activities that are not Isis Conducted Activities.

"***AstraZeneca Full Royalty***" has the meaning set forth in Section 8.8.1.

"***AstraZeneca Indemnitees***" has the meaning set forth in Section 11.2.

"***AstraZeneca-Initiated Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to a Collaboration Plan that are requested by AstraZeneca (including any changes requested or required by a Regulatory Authority).

"***AstraZeneca Know-How***" means any Know-How owned, used, developed by, or licensed to AstraZeneca or its Affiliates, in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary to Develop, register, Manufacture or Commercialize a Product in the Field and such Know-How does not constitute AstraZeneca Background IP.

"***AstraZeneca Patents***" means any Patent Rights owned, used, developed by, or licensed to AstraZeneca or its Affiliates that are invented by AstraZeneca or its Affiliates or licensors in connection with AstraZeneca's performance of its obligations under this Agreement, in each case to the extent Controlled by AstraZeneca or its Affiliates at any time during the Agreement Term that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field and such patents do not constitute AstraZeneca Background IP.

"***AstraZeneca Product-Specific Patents***" means all Product-Specific Patents owned, used, created, developed by, or licensed to AstraZeneca or its Affiliates (i) as of the Effective Date, or (ii) arising at any time during the Agreement Term, in each case to the extent (x) Controlled by AstraZeneca or its Affiliates in connection with performance of obligations under this Agreement, and (y) such Product-Specific Patents do not constitute AstraZeneca Background IP.

"***AstraZeneca-Prosecuted Patents***" has the meaning set forth in Section 9.2.5(b).

"***AstraZeneca Supported Pass-Through Costs***" means [***].

"***AstraZeneca Technology***" means AstraZeneca's interest in Jointly-Owned Collaboration Technology, AstraZeneca Product-Specific Patents, AstraZeneca Know-How, AstraZeneca Patents, including AstraZeneca Background Intellectual Property, and any trademarks described in Section 6.1.8, owned, used, developed by, or licensed to AstraZeneca or its Affiliates that are necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Audit***" has the meaning set forth in Section 11.7.6.

"***Audit Report***" has the meaning set forth in Section 8.11.

"***Bankruptcy Code***" has the meaning set forth in Section 12.2.5(b).

"***BMT Patient***" has the meaning set forth in Section 1.2.3(b).

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, US and London, England are open for business.

"***Calendar Quarter***" means a period of three consecutive calendar months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2012, the Effective Date) and ending on December 31.

"***CDA***" has the meaning set forth in Section 13.2.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control Event***" means any (a) direct or indirect acquisition of all or substantially all of the assets of Isis, (b) direct or indirect acquisition by a Person, or group of Persons acting in concert, of [***]% or more of the voting equity interests of Isis, (c) tender offer or exchange offer that results in any Person, or group of Persons acting in concert, beneficially owning [***]% or more of the voting equity interests of Isis, or (d) merger, consolidation, other business combination or similar transaction involving Isis, pursuant to which any Person owns all or substantially all of the consolidated assets, net revenues or net income of Isis, taken as a whole, or which results in the holders of the voting equity interests of Isis immediately prior to such merger, consolidation, business combination or similar transaction ceasing to hold [***]% or more of the combined voting power of the surviving, purchasing or continuing entity immediately after such merger, consolidation, other business combination or similar transaction, in all cases where such transaction is to be entered into with any Person other than AstraZeneca or its Affiliates.

"***CMO***" means a Third Party primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization of pharmaceutical products.

"***Claims***" has the meaning set forth in Section 11.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, a Registration-Directed Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA, JNDA or other similar marketing application.

"***Collaboration Plan***" means (i) the STAT3 Research and Development Plan, (ii) the [***] Research and Development Plan, or (iii) any Oncology Research and Development Plan.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for the Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting the Product in each country.

"***Commercializing Party***" means (a) AstraZeneca, with respect to a Product that is being Developed and Commercialized by or on behalf of AstraZeneca, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means that level of efforts and resources, at the relevant point in time, commonly used in the pharmaceutical industry for a product of similar commercial potential at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and/or medical factors. Without limiting any of the foregoing, (A) Commercially Reasonable Efforts as it applies to AstraZeneca's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the (i) AstraZeneca Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein, and (ii) activities set forth in each

Integrated Product Plan; and (B) Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to perform the Isis Conducted Activities under each Collaboration Plan in accordance with the timelines set forth therein.

"***Competitive Infringement***" has the meaning set forth in Section 9.5.1.

"***Completion of the IND-Enabling Toxicology Studies***" means [***].

"***Compound***" means (i) an [***] Compound, (ii) a STAT3 Compound, or (iii) an Oncology Compound.

"***Confidential Information***" means any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed by the Disclosing Party or otherwise received or accessed by the Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by

written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(a) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(b) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(c) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided*, *however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than AstraZeneca Supported Pass-Through Costs in the case of AstraZeneca), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***CSID Criteria***" means the candidate selection identification criteria used by AstraZeneca to seek internal approval to advance a Development Candidate.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of a Product to seek Approval for additional indications for such Product.

"***Development Candidate***" means, in the case of the [***] Program or an Oncology Collaboration Program, a Compound that AstraZeneca has determined meets AstraZeneca's CSID Criteria and which it selects as ready to start IND-Enabling Toxicology Studies as provided herein.

"***Disclosing Party***" has the meaning set forth in Section 13.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"***Discontinued Target***" has the meaning set forth in Section 3.3.7(a).

[***]

"***DLBCL Patient***" means a patient that has diffuse large B-cell lymphoma.

"***Draft Report***" means a report containing the pharmacology, toxicology, and pharmacokinetic data generated from an IND-Enabling Toxicology Study.

"***Drug Safety Information Agreement***" means an agreement between the Parties which outlines the requirements and responsibilities for drug safety reporting and monitoring for ISIS-STAT3$_{Rx}$, as described in Section 7.3.1.

"***Durable Response***" has the meaning set forth in Section 1.2.3(b).

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union from time to time.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means (i) with respect to the practice of the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents, (A) the prophylactic or therapeutic use or form of administration in humans or animals of a STAT3 Product or Oncology Product for any indication, and (B) the prophylactic or therapeutic use or form of administration in humans or animals of an [***] Product in the AstraZeneca [***]-Field, and (ii) with respect to the practice of the Isis Product-Specific Patents, (Y) the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of a STAT3 Product or Oncology Product for any indication, and (Z) the prophylactic, therapeutic or diagnostic use or form of administration in humans or animals of an [***] Product in the AstraZeneca [***]-Field.

"***First Commercial Sale***" means the first sale of a Product by AstraZeneca, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of such Product has been obtained in such country.

"***FTE***" means the efforts of one or more employees of Isis equivalent to the efforts of one full-time Isis employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year based upon a total of one thousand seven hundred and ten (1710) hours per year of work on the development program.

"***FTE Rate***" means [***].

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 4.6.1 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Gene Target***" means (i) a Licensed Target, or (ii) an Oncology Target. The term "***Gene Targets***" means collectively Licensed Targets and Oncology Targets.

"***Government Official***" means any Person employed by or acting on behalf of a government, government-controlled entity or public international organization; any political party, party official or candidate; any Person who holds or performs the duties of an appointment, office or position created by custom or convention; and any Person who hold himself out to be the authorized intermediary of any of the foregoing.

"[***]" means a patient enrolled in a Clinical Study of ISIS-STAT3$_{Rx}$ that [***].

"[***]" means a Clinical Study in [***].

"***High Response Outcome***" has the meaning set forth in Section 1.2.3(a).

"***ICC***" has the meaning set forth in Section 14.1.3(a).

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND, including API manufacturing to support such activities.

"***IND Support Package***" means the package of written materials that will support AstraZeneca's IND filings, which package will include Draft Reports generated from the studies listed on APPENDIX 11.

"***Indemnified Party***" has the meaning set forth in Section 11.3.

"***Indemnification Claim Notice***" has the meaning set forth in Section 11.3.

"***Indication***" means [***].

"***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by law to be disclosed on the invoice.

"***Initial Supply***" has the meaning set forth in Section 4.6.1(b).

"***Initiation***" or "***Initiate***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 7.1.1.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis [***]-Field***" has the meaning set forth in Section 5.1.3(a)(ii).

"***Isis [***]-Field ASO***" has the meaning set forth in Section 5.1.3(a)(ii).

"***Isis [***]-Field ASO Licensee***" has the meaning set forth in Section 9.2.4(a).

"***Isis Conducted Activities***" means the research, pre-clinical and/or clinical activities for which Isis is designated as responsible under any Collaboration Plan.

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and

Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on APPENDIX 7 attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 8.9.1(a).

"***Isis Indemnitees***" has the meaning set forth in Section 11.1.

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 7.2.

"***Isis Know-How***" means any Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Isis' interest in any Jointly-Owned Collaboration Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Isis' interest in any Jointly-Owned Collaboration Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on APPENDIX 8 attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Owned Patents***" has the meaning set forth in Section 10.2.2.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on APPENDIX 9 attached hereto.

"***Isis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 9.1.3(a).

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of a Collaboration Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights that claim or cover Jointly-Owned Collaboration Know-How.

"***Jointly-Owned Collaboration Technology***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

[***]

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Knowledge***" means a Party's and its Affiliates' good faith, actual understanding of the facts and information as of the Effective Date; *provided that*, with respect to information regarding the status of Patent Rights or other intellectual property rights, "*Knowledge*" means such Party's or its Affiliate's good faith, actual understanding of the facts and information as of the Effective Date after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

"***Lead Candidate"*** means, in the case of the [***] Program or an Oncology Collaboration Program, a Compound that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 4.

"***Lead Candidate Data Package***" means, with respect to a Lead Candidate, the data package Isis presented to its Research Management Committee to approve a Compound as the Lead Candidate; *provided* such package contains the same level of detail as the data packages Isis currently presents to its Research Management Committee to approve Isis' own internal development candidates and is consistent with relevant Collaboration Plan agreed by the JSC for the [***] or the Oncology Target, as applicable.

"***Licensable [***] Product-Specific Patents***" means Patent Rights Controlled by Isis or any of its Affiliates on or after the Effective Date claiming both:

(i) a sequence-based composition of matter that generically encompasses the [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds), or methods of using the [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds), as a prophylactic, therapeutic or diagnostic but, in each case, does not claim the specific [***] Development Candidate or an [***] Lead Compound (or any [***] Product incorporating such [***] Development Candidate or any [***] Lead Compounds) (the exact sequence and chemistry); *and*

(ii) an Isis [***]-Field ASO, or method for [***] of Isis [***] Field ASOs for the treatment of a [***] disease.

"***Licensed CMO***" has the meaning set forth in Section 6.1.4(a)(ii).

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Isis' interest in Jointly-Owned Collaboration Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Collaboration Patents.

"***Licensed Target***" means (i) STAT3, or (ii) [***]. The term "***Licensed Targets***" means collectively STAT3 and [***].

"***Licensed Technology***" means any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 6.1.8, to the extent necessary or useful to Develop, register, Manufacture or Commercialize a Product in the Field.

"***Losses***" has the meaning set forth in Section 11.1.

"***Low Response Outcome***" has the meaning set forth in Section 1.2.3(b).

"***MAA***" means a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for a Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means the Approval of an MAA by the EMA for a Product in any country in the EU.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, importing and keeping, for pre-clinical and clinical purposes, of API or a Product in finished form.

"Material Anti-Corruption Law Violation" means a violation of an Anti-Corruption Law relating to the subject matter of this Agreement which would if it were publicly known, in the reasonable view of AstraZeneca, have a material adverse effect on Isis or on the reputation of AstraZeneca because of its relationship with Isis.

"***Medium Response Outcome***" has the meaning set forth in Section 1.2.3(b).

"***Minimum Third Party Payments***" means ***].

[***]

"***MSA***" has the meaning set forth in Section 4.6.1(d).

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***Net Sales***" means the gross invoiced amount on sales of Products by or on behalf of AstraZeneca, its Affiliates, and Sublicensees to Third Parties (which will include Distributors) after deduction of the following amounts, to the extent taken:

(a) normal and customary trade, quantity or prompt settlement discounts (including chargebacks and allowances) actually allowed;

(b) amounts repaid or credited by reason of rejection, returns or recalls of goods, rebates or *bona fide* price reductions determined by AstraZeneca or its Affiliates in good faith;

(c) rebates and similar payments made with respect to sales paid for by any governmental or regulatory authority such as, by way of illustration and not in limitation of the Parties' rights hereunder, Federal or state Medicaid, Medicare or similar state program in the United States or equivalent governmental program in any other country;

(d) any invoiced amounts which are not collected by AstraZeneca or its Affiliates, including bad debts;

(e) excise taxes, Indirect Taxes, customs duties, customs levies and import fees imposed on the sale, importation, use or distribution of the Products; and

(f) any other similar and customary deductions that are consistent with generally accepted accounting principles, or in the case of non-United States sales, other applicable accounting standards; and

after deduction of (i) an allowance for transportation costs, distribution expenses, special packaging and related insurance charges equal to [***] ([***]) of the amount arrived at after application of the provisions of items (a) through (f) above; and (ii) the actual cost paid by AstraZeneca, its Affiliates or Sublicensees for Devices.

Net Sales will be calculated using AstraZeneca's internal audited systems used to report such sales as adjusted for any of the items above not taken into account in such systems. Deductions pursuant to subsection (d) above will be taken in the Calendar Quarter in which such sales are no longer recorded as a receivable. As used above, the term *"Device"* means any device approved by a Regulatory Authority for use with a Product that is necessary to administer the Product to a patient (i.e. without such device the Product cannot be delivered by any other means or methods).

If a Product is sold as part of a Combination Product (as defined below), the Net Sales from such Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product by the fraction A/(A+B), where A is the standard sales price of the ready-for-sale form of the Product, containing the same amount of Compound as the sole active ingredient as the Combination Product in question, in the given country when sold separately in finished form; and B is the standard sales price of the ready-for-sale form of the product containing the same amount of the other therapeutically active ingredient(s) that is contained in the Combination Product in question, in the given country, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period. In the event, however, that if, in a specific country either or both of the Compound and the other therapeutically active ingredient in such Combination Product are not sold separately in such country, a market price for such Product and such other active ingredient shall be negotiated by the Parties in good faith for the purposes of performing the calculation above to determine royalty payments on the Net Sales from such Combination Product. As used above, the term

"Combination Product" means a Product that includes at least one additional therapeutically active ingredient (whether coformulated or copackaged) and is not a Compound.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Non-Transferring Party***" has the meaning set forth in Section 14.3.

"***Oncology Compound***" means any ASO that is designed to bind to the RNA that encodes an Oncology Target, where such ASO is discovered by Isis prior to the Effective Date or in the performance of an Oncology Research and Development Plan.

"***Oncology Collaboration***" means the conduct of the Oncology Collaboration Programs in accordance with this Agreement.

"***Oncology Collaboration Program***" means a discovery research program focused on discovering Oncology Compounds to select an Oncology Development Candidate in accordance with the applicable Oncology Research and Development Plan.

"***Oncology Collaboration Term***" has the meaning set forth in Section 3.2.2.

"***Oncology Development Candidate***" means a Development Candidate selected by AstraZeneca arising out of the work conducted under an Oncology Research and Development Plan.

"***Oncology Development Candidate Decision Deadline***" has the meaning set forth in Section 3.3.3.

"***Oncology Lead Candidate***" means Lead Candidate designated by Isis as a potential Oncology Development Candidate

"***Oncology Product***" means a finished product containing an Oncology Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"***Oncology Research and Development Plan***" means any research and/or development plan attached hereto as Appendix 3 for an Oncology Collaboration Program focused on a particular Oncology Target as amended from time to time in accordance with this Agreement.

"***Oncology Target***" means (i) any of the three Reserved Targets that are selected under Section 3.3.6 to be the subject of an Oncology Collaboration Program, (ii) any Substitute Target, or (iii) any oncology target added to this Agreement under Section 2.2.4.

"***Option***" has the meaning set forth in Section 3.5.

"***Option Deadline***" has the meaning set forth in Section 3.5.

"***Outcome Notice***" has the meaning set forth in Section 1.2.3(e).

"***Participating Parties***" has the meaning set forth in Section 9.2.4(b).

"***Party***" or "***Parties***" means AstraZeneca and Isis individually or collectively.

"***Party Representatives***" has the meaning set forth in Section 11.7.1.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions in connection with the Isis Conducted Activities approved by AstraZeneca, such approval not to be unreasonably withheld or delayed.

"***Person***" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 7.3.2.

"***Phase 1 Trial***" means the initial clinical testing of a Product in humans (first-in-humans study) with the intention of gaining a preliminary assessment of the safety of such Product. "*Phase 1 Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 1 Trial*" or "*Phase 1 Study*."

"***Phase 1/2 Trial***" means Isis' ongoing Clinical Study described in the STAT3 Research and Development Plan, including the expansion cohort for such trial.

"***Phase 1/2 Trial Data Package***" means, with respect to the Phase 1/2 Trial, the listing and tables of safety and efficacy data, radiographic scans of tumor assessments, radiologist reports and summary of biomarker or other assay data that was mutually agreed by Isis and AstraZeneca.

"***Phase 2 Trial***" means any Clinical Study in a single tumor type or enriched for a tumor type that is intended to show safety and efficacy (which efficacy may be shown by a biomarker or other assay) in the target population, at the intended clinical dose or doses or range of doses, on a sufficient number of subjects and for a sufficient period of time to confirm the optimal manner of use of the Product prior to initiation of the Phase 3 Trials, and which itself provides sufficient evidence of safety and efficacy to be included as a supportive study to the Phase 3 Trial in filings with Regulatory Authorities. "*Phase 2 Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 2 Trial*," "*Phase 2a Trial*," *Phase 2b Trial*," "*Phase 2 Study*," *Phase 2a Study*" or "*Phase 2b Study*."

"***Phase 3 Trial***" or "***Registration-Directed Trial***" means a pivotal Clinical Study (whether or not denominated as a "Phase 3" Clinical Study under applicable regulations) in human patients that is of the size and design intended to establish that a Product is safe and effective for its intended

use; to define warnings, precautions and adverse reactions that are associated with the Product in the dosage range to be prescribed; and is intended to support Approval of such Product. "*Phase 3 Trial*" or "*Registration-Directed Trial*" includes any clinical study designated under a Collaboration Plan as a "*Phase 3 Trial*," "*Phase 3 Study*" or "*Registration Trial*."

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of one or more Compounds, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of the Product and whether the Product has a desired effect.

"***Prior Agreements***" means the agreements listed on APPENDIX 10 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, as applicable (i) a STAT3 Product, (ii) an [***] Product, or (iii) an Oncology Product.

"***Product-Specific Patents***" means:

(A) with respect to [***] Products: (i) Assignable [***] Product-Specific Patents; and (ii) Licensable [***] Product-Specific Patents, or

(B) with respect to STAT3 Products and Oncology Products: Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date claiming: (i) the specific composition of matter of a STAT3 Product or Oncology Product, or (ii) methods of using such a Product as a prophylactic, therapeutic or diagnostic.

"***Proposed Substitute Target***" has the meaning set forth in Section 3.3.7(a).

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "*Prosecution and Maintenance*" or "*Prosecute and Maintain*" will not include any other enforcement actions taken with respect to a Patent Right.

"***R&D Research and Development Plan***" means collectively the (i) STAT3 Research and Development Plan, and (ii) [***] Research and Development Plan.

"***Receiving Party***" has the meaning set forth in Section 13.1.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"Regulatory Documentation" means any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize a Product in the Field.

"***Relevant Authority***" means any court or government body, whether national, supra-national, federal, state, local, foreign or provincial, including any political subdivision thereof, including any department, commission, board, bureau, agency, or other regulatory or administrative governmental authority or instrumentality, and further including any quasi-governmental Person or entity exercising the functions of any of these.

"***Research***" means conducting the research activities with Compounds as set forth in a Collaboration Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***Reserved Target***" means any gene target reserved for potential selection as an Oncology Target in accordance with Section 3.3.5.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***Royalty Period***" has the meaning set forth in Section 8.8.2(a).

"***Safety Concern***" has the meaning set forth in Section 1.2.3(d).

"***Senior Representatives***" has meaning set forth in Section 14.1.1.

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under a Collaboration Plan.

"***STAT3***" means the gene, signal transduction and activation of transcription 3 (GenBank accession # NM_139276.2; Gene ID: 6774) (also known as acute-phase response factor (APRF)), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***STAT3/[***] Collaboration***" means the conduct of the STAT3 Program and the [***] Program in accordance with this Agreement.

"***STAT3 Compound***" means any ASO that is designed to bind to the RNA that encodes STAT3, where such ASO is discovered or Controlled by Isis prior to the Effective Date or in the performance of the STAT3 Research and Development Plan, including the Compound known as ISIS-STAT3$_{Rx}$ (also referred to by compound number ISIS 481464).

"***STAT3 Product***" means any finished product containing a STAT3 Compound as an active pharmaceutical ingredient (including any salt, hydrate, solvate, or prodrug thereof).

"***STAT3 Program***" means the research and/or development program for STAT3 Products under this Agreement.

"***STAT3 Research and Development Plan***" means the research and/or development plan for the STAT3 Program (initially as attached hereto as Appendix 2) as amended from time to time in accordance with this Agreement.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or AstraZeneca Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Substitute Notice***" has the meaning set forth in Section 3.3.7(a).

"***Substitute Target***" has the meaning set forth in Section 3.3.7(b).

"***Target Encumbrances***" has the meaning set forth in Section 3.3.5.

"***Target Knock-Down***" has the meaning set forth in Section 1.2.3(c).

"***Target Sanction***" means the stage at which an Oncology Target has demonstrated sufficient therapeutic potential in pre-clinical disease models and has received the recommendation of the JSC to expend resources to identify an Oncology Development Candidate, all in accordance with the JSC's standard

processes.

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Claims***" has the meaning set forth in Section 11.1.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between a Party and a Third Party that relate to a Product or a Gene Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transferring Party***" has the meaning set forth in Section 14.3.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

STAT3 Research and Development Plan and [***] Research and Development Plan

[***]

APPENDIX 3

Oncology Research and Development Plan

[***]

APPENDIX 4

Isis' Lead Candidate Checklist

[***]

APPENDIX 5

Examples (not an exhaustive list) Illustrating Separate Indications

[***]

APPENDIX 6

Isis In-License Agreements

(Relevant to the R&D Research and Development Plan as of the Effective Date)

[***]

APPENDIX 7

Isis Core Technology Patents

[***]

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APPENDIX 8

Isis Manufacturing and Analytical Patents

[***]

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APPENDIX 9

Isis Product-Specific Patents

[***]

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APPENDIX 10

Prior Agreements

[***]

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APPENDIX 11

IND Support Package

[***]

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SCHEDULE 3.3.6

[***]

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SCHEDULE 4.1.1

JSC GOVERNANCE

(a) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(d) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at AstraZeneca's facilities outside of the U.S.). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of the relevant Gene Target.

(e) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 4.1.3,

Section 9.1.3 and Section 14.1, as applicable.

(f) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Isis members and AstraZeneca members, and record such recommendations in the minutes of the applicable JSC meeting.

(g) The JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JSC dissolves.

SCHEDULE 4.1.3(C)

AstraZeneca's Performance Metrics

[***]

SCHEDULE 4.2

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(h) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Collaboration Plans;

(i) Organizing each JSC meeting, including agendas, drafting minutes, and publishing final minutes;

(j) Supporting the co-chairs of the JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(k) Preparing status and progress reports on the above as determined necessary by the JSC;

(l) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 7.2; and

(m) Ensuring proper approval of publications prior to submission as required in Section 13.4.

(n) Review Material Transfer Agreements.

SCHEDULE 4.6.1

Isis' Fully Absorbed Cost of Goods Methodology

[***]

SCHEDULE 4.6.1(d)

Manufacturing Services Agreement Principles

[***]

Schedule 4.7

AstraZeneca Bioethics Policy

[***]

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4 AND 240.24B-2

NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.,

AND

BIOGEN IDEC MA INC.

NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 10th day of December, 2012 (the "***Effective Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **BIOGEN IDEC MA INC.**, a Massachusetts corporation, having its principal place of business at 14 Cambridge Center, Cambridge, MA 02142 ("***Biogen Idec***"). Biogen Idec and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis possesses certain Patent Rights, Know-How, technology and expertise with respect to antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of antisense therapeutics;

WHEREAS, Biogen Idec has expertise in developing and commercializing human therapeutics, and Biogen Idec is interested in developing and commercializing antisense therapeutics for up to three gene targets;

WHEREAS, Biogen Idec desires Isis to (i) identify a development candidate for each of the three gene targets, (ii) develop the development candidates through completion of the first clinical trial designed to demonstrate proof of mechanism or proof of therapeutic benefit, and (iii) provide Biogen Idec an option to obtain an exclusive license under this Agreement to develop, manufacture and commercialize Products in the Field.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
RESEARCH AND DEVELOPMENT

1.1. **Collaboration Overview**. The intent of the Collaboration is for Isis to (i) conduct Collaboration Programs for each of the three Collaboration Targets, (ii) generate at least one Development Candidate for each Collaboration Program; (iii) advance each Development Candidate through the completion of the first PoC Trial under the applicable Collaboration Program; and (iv) allow Biogen Idec the opportunity to exercise an Option to further Develop and ultimately Commercialize Compounds and Products under such Collaboration Program under an exclusive license from Isis. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights

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and obligations of each Party under this Agreement, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2. **Collaboration Programs**. Subject to and in accordance with the terms of this Agreement, Isis and Biogen Idec will be responsible for conducting three programs to Discover, Develop, Manufacture and Commercialize Products (each, a ***"Collaboration Program"***), each to be focused on a different Collaboration Target, pursuant to which:

1.2.1. Isis will use its Commercially Reasonable Efforts to (i) conduct drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according to the applicable Collaboration Program Research Plans to achieve Target Sanction status, (ii) identify a Development Candidate for the applicable Collaboration Program, and (iii) conduct drug development activities for each Development Candidate through completion of the first PoC Trial under a Collaboration Program in accordance with the applicable Development Plan; *provided* that Isis will not be required to commence work on more than [***] Collaboration Programs in any rolling [***] month period; and

1.2.2. following each Option exercise, Biogen Idec will use its Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each Collaboration Program for which Biogen Idec has exercised an Option in accordance with this Agreement.

1.3. **High Interest Targets.**

1.3.1. **High Interest Target List.** Subject to the replacement rights set forth in Section 1.3.2 below, the Parties will maintain, through the Neurology JSC, a list of mutually-agreed gene targets that are of high interest as potential Collaboration Targets (each such target, a ***"High Interest Target"*** and such list the ***"High Interest Target List"***) according to the following procedure:

(a) As of the Effective Date, the Parties have agreed upon a written list containing the initial [***] High Interest Targets;

(b) On [***], the number of High Interest Targets on the High Interest Target List will be reduced to [***] High Interest Targets. By [***], Biogen Idec will provide Isis a written notice designating the [***] gene targets (from the [***] gene targets listed on the High Interest Target List) that will remain as High Interest Targets;

(c) Each time after the Effective Date that a Collaboration Target is designated under Section 1.4.1, Section 1.4.2 or Section 2.3, the number of High Interest Targets for purposes of the High Interest Target List will be reduced by [***], and the High Interest Target so designated as a Collaboration Target will no longer be a High Interest Target for purposes of the High Interest Target List; and

(d) Upon the earlier of the (i) [***]; and (ii) [***], the High Interest Target List will be dissolved and no gene target will thereafter be a High Interest Target.

1.3.2. **Replacement.** At any time prior to the [***], Biogen Idec may, in accordance with the terms of this Agreement, propose a replacement of a High Interest Target on the High Interest Target List, in which case Isis and Biogen Idec will mutually agree to replace such High Interest Target with a different gene target for purposes of the High Interest Target List, provided, however that, Isis may only choose not to agree to replace a High Interest Target on the High Interest Target List with a gene target proposed by Biogen Idec if, at the time of such proposal, [***], a ***"Dispositive Disagreement Condition"***). If Isis notifies Biogen Idec within [***] days after receipt of Biogen Idec's request to add a gene target as a High Interest Target that a Dispositive Disagreement Condition exists with respect to such gene target, the members of the Neurology JSC will discuss such Dispositive Disagreement Condition and work together in good faith to promptly repeat a similar process as set forth in this Section 1.3.2 until Biogen Idec and Isis have selected a replacement target. With respect to any replacement under this Section 1.3.2, (A) the gene target substituted-in will thereafter be a High Interest Target on the High Interest Target List; and (B) the gene target removed will no longer be a High Interest Target on the High Interest Target List.

1.3.3. **Replacement Limit.** Notwithstanding the foregoing, the Parties may not replace more than [***] High Interest Target in any rolling [***] month period, without Isis' written consent (the "***Replacement Limit***"); *provided* replacing-in another gene target under Section 1.5.6 will not count for purposes of calculating the Replacement Limit.

1.4. **Collaboration Targets**.

1.4.1. **Designation.** The maximum number of Collaboration Targets will be three. Subject to the substitution rights set forth in Section 1.4.2 below, as of the Effective Date, the first Collaboration Target is [***]. At any time from [***] through [***], Biogen Idec may designate the second Collaboration Target from the High Interest Target List, and at any time from [***] through the [***] anniversary of the Effective Date, Biogen Idec may designate the third Collaboration Target from the High Interest Target List.

1.4.2. **Substitution**. With respect to any Collaboration Target that [***], Biogen Idec may substitute such Collaboration Target with a gene target from the High Interest Target List by providing written notice to Isis designating the gene target it is removing as a Collaboration Target and the High Interest Target from the High Interest Target List it is now designating as a Collaboration Target. Upon such substitution, (i) Isis will begin a Collaboration Program on the High Interest Target so substituted-in as a Collaboration Target; and (ii) Isis' obligations, and Biogen Idec's rights, under this Agreement with respect to the removed gene target will terminate, and the removed gene target will no longer be a

Collaboration Target. *Notwithstanding the foregoing*, Biogen Idec may not substitute more than [***] Collaboration Target (the ***"Substitution Limit"***), without Isis' written consent; *provided* substituting-in an Accelerated Target under Section 2.3 or another High Interest Target under Section 1.5.6 or Section 10.2.4(a) will not count for purposes of calculating the Substitution Limit.

1.5. **Isis' Research and Development Responsibilities**.

1.5.1. **Collaboration Program Research Plans**. Isis will carry out its drug discovery efforts for each Collaboration Program pursuant to the applicable Collaboration Program Research Plan in a manner consistent with its internal practices for other gene targets with the goal of achieving Target Sanction and identifying a Development Candidate for the applicable Collaboration Program as soon as practicable. Isis will update each Collaboration Program Research Plan as needed and submit it to the Neurology JSC for its review and comment. In addition, once a Collaboration Program achieves Target Sanction, the Neurology JSC will begin preliminary discussions regarding an appropriate development plan for the contemplated Development Candidate under such Collaboration Program.

For each Collaboration Program Isis will provide the Neurology JSC:

(a) promptly (but no later than [***]) following the designation of a Collaboration Target, an initial research plan delineating the experiments that should be conducted to achieve Target Sanction for such Collaboration Target; and

(b) the initial plan approved by Isis' RMC in connection with a Target Sanction under a Collaboration Program to identify a Development Candidate, as may be modified from time to time to address the discovery, research and optimization activities Isis

will conduct under the applicable Collaboration Program (together, each such plan under Sections 1.5.1(a) and 1.5.1(b), a ***"Collaboration Program Research Plan"***).

Isis will reasonably consider the comments provided by the Neurology JSC on each Collaboration Program Research Plan.

1.5.2. Development Candidates; Development Plans; Option Acceleration.

(a) Isis will notify Biogen Idec in writing within 30 days of designating a Development Candidate and will provide Biogen Idec the applicable Development Candidate Data Package. For each Development Candidate under a Collaboration Program within [***] after designation of such Development Candidate, the Parties will mutually agree on an appropriate development plan for such Development Candidate through completion of the first PoC Trial (each, a ***"Development Plan"***) and will update SCHEDULE 5.1.1 to add Specific Performance Milestone Events

related to Biogen Idec's Development and Commercialization of the Development Candidate following Option exercise, which Specific Performance Milestone Events will be generally consistent with Biogen Idec's development timelines for its other drug development programs of similar stage and market potential. Prior to an Option exercise, in the event the Parties are unable to agree upon the POC Trial Design for a particular Collaboration Program, in lieu of mediation pursuant to Section 12.1.2, [***] will have final decision-making authority with respect to the POC Trial Design. If the Parties are unable to agree upon the Specific Performance Milestone Events for a particular Collaboration Program, the matter will be resolved in accordance with Section 12.1, including, for the avoidance of doubt, mediation pursuant to Section 12.1.2, if necessary. Isis will update each Development Plan as needed, but at least once Annually, and submit it to the Neurology JSC for its review and comment, provided, however, [***] must be unanimously agreed to by the Neurology JSC.

(b) Within [***] after designation of such Development Candidate, the Parties will mutually agree on the expected cost for Isis to conduct the work specified in the applicable Development Plan (each, a ***"Cost Estimate"***), and appropriate [***] and [***] milestone payments equal to (i) [***]; plus (ii) [***]. The Parties will negotiate in good faith using the Isis/Biogen Preexisting Development Agreements as a basis for costs estimates. As part of this process, Isis will provide Biogen Idec with a good faith estimate of the cost to conduct the work necessary to develop such Development Candidates under the applicable Development Plan using a similar methodology as used under the Isis/Biogen Preexisting Development Agreements.

(c) Isis will not be required to conduct any Development activities for a Development Candidate if Isis and Biogen Idec have not mutually agreed on an initial Development Plan, Specific Performance Milestone Events and the corresponding Cost Estimates pursuant to this Section 1.5.2.

(d) If the PoC Trial for a Collaboration Program will be [***] or more, or require more than [***], then, if Isis provides to Biogen Idec the notice described in the following sentence, Isis will not be required to conduct such PoC Trial for such Collaboration Program. Isis will notify Biogen Idec within [***] after finalization of the initial PoC Trial Design (or each time there is a material change thereto) for a Collaboration Program pursuant to Section 1.5.2(a) if Isis elects not to conduct such PoC Trial for such Collaboration Program (such notice, an ***"Option Acceleration Notice"***). If Isis has delivered an Option Acceleration Notice as provided in this Section 1.5.2(d), Biogen Idec will have [***] from its receipt of the data generated under the [***] for the first Phase 1 Trial

for such Collaboration Program (an ***"Option Acceleration Deadline"***) to exercise its Option for the applicable Collaboration Program. If Biogen Idec does not exercise its Option for the applicable Collaboration Program by the applicable Option Acceleration Deadline, Biogen Idec's Option under Section 3.1 with respect to such Collaboration Program will expire and such Collaboration Program will terminate. In addition, after Biogen Idec's receipt of an Option Acceleration Notice with respect to a particular Collaboration Program, Biogen Idec will have final decision-making authority with respect to [***] to the extent related to the PoC Trial for the applicable Collaboration Program.

(e) The Neurology JSC will attach each Development Plan and associated Cost Estimates to the minutes of the Neurology JSC for the first meeting following agreement regarding such Development Plan and Cost Estimates by the Parties.

1.5.3. Drug Development. Isis will use Commercially Reasonable Efforts to conduct all activities under each Development Plan on the timeline set forth in the applicable Development Plan, including the following Development activities under this Agreement:

(a) Subject to Section 1.6 below, Develop each Development Candidate through the completion of the first PoC Trial; *provided, however,* Isis may discontinue such Development if at any time after having consulted, and having given good faith consideration to the recommendations of the Neurology JSC and a mutually-agreed Third Party expert, Isis in good faith believes that continuing such Development would (i) pose an unacceptable risk or threat of harm in humans, or (ii) violate any Applicable Law, ethical principles, or principles of scientific integrity. Prior to discontinuing Development of a Development Candidate, Isis will provide Biogen Idec with reasonable advance notice of such discontinuation, including the grounds for Isis' determination. If Isis elects to discontinue Development of a Development Candidate pursuant to this Section 1.5.3(a), Biogen Idec may, in its discretion, elect to continue Development of the Development Candidate by providing Isis with written notice of Biogen Idec's exercise of the Option within 90 days after Isis' written notice to Biogen Idec of such discontinuation. If Biogen Idec timely exercises its Option under this Section 1.5.3(a), then [***]. If Biogen Idec does not timely exercise its Option under this Section 1.5.3(a), then the Option will expire.

(b) ***Phase 1 Trials***. Each Phase 1 Trial will be conducted in accordance with the applicable Phase 1 Trial Design set forth in the applicable Development Plan. Isis will keep Biogen Idec informed of the progress and status of each Phase 1 Trial. When Isis [***] a Phase 1 Trial, Isis will notify Biogen Idec in writing within 30 days. Isis will provide

Biogen Idec with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(c) ***PoC Trial***. Each PoC Trial will be conducted in accordance with the PoC Trial Design set forth in the applicable Development Plan. Isis will keep Biogen Idec informed of the progress and status of each PoC Trial. When Isis [***] a PoC Trial under the applicable Development Plan, Isis will notify Biogen Idec in writing within 30 days after such measurement. Isis will provide Biogen Idec with the [***] as soon as practicable after such notice. If Biogen Idec exercises its Option prior to the Initiation of the first PoC Trial for a Collaboration Program, Biogen Idec will keep Isis informed of the progress and status of the PoC Trial for such Collaboration Program. When Biogen Idec completes such PoC Trial, Biogen Idec will notify Isis in writing within 30 days after such completion, and will provide Isis with [***] as soon as practicable after such notice.

1.5.4. **Briefing of the Neurology JSC; Conduct of Research and Development**. At each regularly scheduled meeting of the Neurology JSC, Isis will provide to the Neurology JSC progress updates on (i) the status of each Collaboration Program generally; (ii) Isis' research activities on the High Interest Targets conducted pursuant to Section 2.3; (iii) activities conducted under each Collaboration Program Research Plan, including progress towards Target Sanction or Development Candidate, as applicable; and (iv) activities conducted under the Development Plans for each Development Candidate, in each case, together with a summary of data associated with Isis' research and/or Development activities for each Collaboration Program. Isis will conduct its work under each Collaboration Program in a good scientific manner, and in compliance with all applicable good laboratory practices and cGMP, and all Applicable Laws.

1.5.5. **Clinical Supplies by Isis**. Isis, at its expense, will supply API (on its own or through a CMO approved by Biogen Idec) and Clinical Supplies to support the Research and Development activities under each Collaboration Program Research Plan and each Development Plan through Option Exercise. If Biogen Idec exercises an Option at least [***] prior to the planned Initiation of the PoC Trial for the applicable Collaboration Program, Biogen Idec may elect to either have (a) Isis supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen Idec), in which case Biogen Idec will pay Isis an amount equal to [***], or (b) a CMO supply Clinical Supplies for such PoC Trial in accordance with the Manufacturing Agreement entered into with such CMO. If Biogen Idec exercises an Option prior to, but less than [***] before, the planned Initiation of the PoC Trial for the applicable Collaboration Program, Isis will supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen Idec) and Biogen Idec will pay Isis an amount equal to [***].

1.5.6. **Collaboration with Third Parties**. Isis may engage one or more academic or non-profit institutions to conduct work under any Collaboration Program

Research Plan or Development Plan or to conduct drug discovery activities to identify a High Interest Target Development Candidate pursuant to Section 2.3, *provided however* that, (a) with respect to any such academic or non-profit institution engaged to conduct such activities with respect to a Collaboration Target, where such engagement occurs after the date such Collaboration Target is designated, or (b) with respect to any such academic or non-profit institution engaged to conduct such activities with respect to one of the remaining High Interest Targets, where such engagement occurs after the later of [***] or the date such High Interest Target is designated, (i) prior to engaging such academic or non-profit institution to conduct such activities, Isis will consult with Biogen Idec in good faith with respect to the terms of any agreement or amendment to an existing agreement to be entered into with such institution and consider Biogen Idec's comments with respect thereto in good faith and (ii) if Isis enters into any such agreement or amendment on terms objected to by Biogen Idec in a written notice provided to Isis prior to the execution thereof, it shall promptly so notify Biogen Idec, which notice will include a copy of such agreement or amendment, and within 30 days following Biogen Idec's receipt of such notice, Biogen Idec may elect to replace the applicable High Interest Target or Collaboration Target with a different gene target in accordance with the procedures set forth in Section 1.3.2 or Section 1.4.2, as applicable, and such replacement will not be counted for purposes of determining whether Biogen Idec has exceeded the Replacement Limit or Substitution Limit, as applicable.

1.6. **Research and Development Costs and Expenses**.

1.6.1. **Research and Development Costs Paid by Isis**. Until Biogen Idec exercises the Option, Isis will be responsible for all research and Development activities for each Development Candidate under the Collaboration Program Research Plan and Development Plan and, except as otherwise provided under Section 1.6.2(a), all costs and expenses associated therewith.

1.6.2. **Development Costs Paid by Biogen Idec**.

(a) **Before Option Exercise**. Biogen Idec will be responsible for paying any Other Pre-Option Costs and any Additional Plan Costs resulting from Biogen-Initiated Changes. Isis will permit Biogen Idec to review, negotiate (with Isis) and approve the Additional Plan Costs before implementing any Biogen-Initiated Changes. Isis and Biogen Idec will update the applicable Development Plan with any such revised studies and Isis will invoice Biogen Idec for any such approved Additional Plan Costs. Biogen Idec will pay the invoices submitted pursuant to this Section 1.6.2(a) for such approved Additional Plan Costs within 45 days after receipt of the applicable invoice by Biogen Idec.

(b) **After Option Exercise**. After Option exercise, Biogen Idec will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products.

1.7. Drug Discovery and Drug Development Terms.

1.7.1. The term for the conduct of the Drug Discovery Program will begin on the Effective Date and will end upon the earlier of (i) designation of a Development Candidate for each Collaboration Program and (ii) the [***] anniversary of the Effective Date (the ***"Drug Discovery Term"***), *provided however*, that if Isis is still conducting work under a Collaboration Program Research Plan on the date of expiration of the Drug Discovery Term, the Drug Discovery Term will be automatically extended until the earlier of the (a) date on which Isis completes all activities under each such Collaboration Program Research Plan and (b) the [***] anniversary of the Effective Date, and *provided further,* that if, as a result of Isis' breach, Biogen Idec has substituted a High Interest Target for a Collaboration Target pursuant to Section 10.2.4(a), and Isis is conducting activities under the applicable Collaboration Program Research Plan on the date on which the Drug Discovery Term would otherwise expire, the Drug Discovery Term will be extended for a reasonable period of time (not to exceed the [***] anniversary of the date of such substitution) to allow Isis to complete such activities.

1.7.2. The term for the conduct of the Drug Development Program will begin on the designation of the first Development Candidate and will end upon the earlier of (i) completion of the first PoC Trial for a Development Candidate under each Collaboration Program, which the Parties estimate will be approximately [***] years after the Effective Date, (ii) exercise by Biogen Idec of each of its Options for each Collaboration Program; (iii) the termination of the last Collaboration Program; and (iv) mutual agreement of the Parties to terminate the Drug Development Program.

1.7.3. Upon the end of the Drug Discovery Term, subject to Section 1.7.4, (i) Isis will no longer have an obligation to perform any activities under Section 1.5; (ii) any Collaboration Programs that have not reached the Development Candidate stage will no longer be Collaboration Programs and the applicable gene targets associated therewith will no longer be Collaboration Targets; (iii) Isis' obligations and Biogen Idec's rights under this Agreement with respect to such gene target and any ASOs targeting such gene target will then terminate, and Isis will be free to Develop and Commercialize on its own or with a Third Party such gene target and any Compounds targeting such gene target; and (iv) Isis will own any data generated under the Collaboration Program for such gene target and any Compounds targeting such gene target. For clarity, except to the extent explicitly set forth in the foregoing, the expiration of the Drug Discovery Term will not affect Biogen Idec's rights or Isis' obligations with respect to Collaboration Programs under this Agreement that have reached the Development Candidate stage by the end of the Drug Discovery Term, including, but not limited to, Isis' obligation under Section 1.5.3 to Develop each such Development Candidate under the remaining Collaboration Programs through the completion of the first PoC Trial.

1.7.4. If, despite Isis' Commercially Reasonable Efforts, by the end of the Drug Discovery Term, Isis has not designated a Development Candidate for a particular Collaboration Program, then if at any time during the [***] period after the end of the Drug Discovery Term Isis' RMC designates an ASO discovered by Isis that is designed to bind to the RNA that encodes the Collaboration Target that was the subject of such Collaboration Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a "***Carryover Development Candidate***"), then, Isis will notify Biogen Idec and will provide Biogen Idec with the data package presented to Isis' RMC to approve such Carryover Development Candidate. Biogen Idec will then have 30 days from its receipt of such package to elect to enter into an agreement (or amendment to this Agreement) for an option and license under the same terms as set forth in this Agreement (except that no additional upfront payment under Section 6.1 will be due). If, within 30 days after Biogen Idec's receipt of such notice from Isis, Biogen Idec provides Isis with written notice that it accepts such offer from Isis for such Carryover Development Candidate, the Parties will execute an agreement (or amendment to this Agreement) regarding such Carryover Development Candidate containing the same terms as those described herein. If Biogen Idec either notifies Isis that it declines the offer for such Carryover Development Candidate, or Biogen Idec does not provide Isis with written notice during such 30-day period that Biogen Idec accepts such offer from Isis for such Carryover Development Candidate, then Isis will be free to research, develop, manufacture and commercialize such Carryover Development Candidate (and/or any other ASO designed to bind to the RNA that encodes the gene target targeted by such Carryover Development Candidate) by itself or with or for a Third Party.

1.8. Additional Activities Requested by Biogen Idec. If Biogen Idec desires that either Isis or a Third Party [***] or conduct other work to support Approval of a Product, including [***], prior to Option exercise ("***Other Pre-Option Activities***"), subject to Section 1.6.1 and Section 1.6.2, Biogen Idec will pay the costs of conducting such work, including, the cost of Isis' time incurred in performing such work at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in performing such work ("***Other Pre-Option Costs***"). Isis will permit Biogen Idec to review, negotiate (with Isis) and approve the Other Pre-Option Costs prior to conducting any Other Pre-Option Activities. Isis will invoice Biogen Idec directly for any such approved Other Pre-Option Costs incurred by Isis and Biogen Idec will pay the invoices submitted pursuant to this Section 1.8 for such approved Other Pre-Option Costs within [***] after receipt of the applicable invoice by Biogen Idec. In the case where Other Pre-Option Activities are performed by a Third Party, the Parties will arrange for the Third Party to directly bill Biogen Idec and for Biogen Idec to pay such Third Party directly.

1.9. Biogen Idec's Participation in Regulatory Meetings. During the Option Period for each Collaboration Program:

(a) Isis will not initiate discussions with a Regulatory Authority regarding the [***] for a Collaboration Program until Isis and Biogen Idec have mutually agreed upon such [***], as applicable.

(b) To the extent practical, prior to any scheduled meeting with a Regulatory Authority regarding the [***] for a Collaboration Program, (i) the Parties will discuss and mutually agree upon the timing and objectives for such meeting and (ii) Isis will provide Biogen Idec with (A) an invitation to attend at least one pre-meeting rehearsal with Isis and (B) an opportunity to discuss the strategy for such meeting with Isis. In addition, Isis will allow Biogen Idec to participate in any such meeting under the direction of Isis.

(c) In each case, to the extent regarding the [***] for a Collaboration Program, Isis will promptly provide Biogen Idec with (i) final copies of all material correspondence with and submission to any Regulatory Authority promptly following submission thereof, (ii) a copy of material communications received from a Regulatory Authority, and (iii) a copy of the minutes from each meeting with a Regulatory Authority.

(d) Isis will provide Biogen Idec with a draft of all correspondence with and submissions to any Regulatory Authority that materially impact the [***] for a Collaboration Program sufficiently in advance of providing such correspondence or submission to the applicable Regulatory Authority to enable Biogen Idec to have a meaningful opportunity to provide comments on the contents thereof. The contents of such correspondence or submission to any Regulatory Authority must reflect the Development Plan. The Parties will mutually agree on the contents of all such correspondence or submissions; *provided* that if mutual agreement is not obtained prior to a Regulatory Authority's requirement for a response, Isis will consider in good faith including any comments provided by Biogen Idec to such correspondence or submissions.

1.10. **Impact of [***] Development Path**. If the Parties mutually agree to amend a Development Plan where such amended plan contemplates [***], then the Parties will make appropriate changes to the operational terms of this Agreement (e.g., [***]) to reflect such an [***] development plan, consistent with the comparable provisions necessary to support the development plan under the [***].

1.11. **Research and Development Management**.

1.11.1. **Neurology JSC**. The Parties will establish a joint steering committee (the "***Neurology JSC***") to provide advice and make recommendations on the conduct of activities under each Collaboration Program. The Neurology JSC will consist of two representatives appointed by Isis and two representatives appointed by Biogen Idec. Each Neurology JSC member will be a senior scientific staff leader or have other experience and expertise appropriate for the stage of development of

the Collaboration Programs. Each Party will designate one of its two representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of the Neurology JSC. The co-chairs will be responsible for overseeing the activities of the Neurology JSC consistent with the responsibilities set forth in Section 1.11.2. SCHEDULE 1.11.1 sets forth certain Neurology JSC governance matters agreed to as of the Effective Date. The Neurology JSC will determine the Neurology JSC operating procedures at its first meeting, including the Neurology JSC's policies for replacement of Neurology JSC members, policies for participation by additional representatives or consultants invited to attend Neurology JSC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JSC meetings. Isis and Biogen Idec will use reasonable efforts to schedule meetings of the Neurology JSC to take place at the same location and on the same dates as meetings of the joint development and steering committees under the Isis/Biogen Preexisting Development Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses. Once a Development Candidate is designated under a Collaboration Program, the Parties will consider in good faith creating a separate subcommittee of the Neurology JSC to govern the activities under this Agreement with respect to such Collaboration Program.

1.11.2. **Role of the Neurology JSC**. Without limiting any of the foregoing, subject to Section 1.11.3, the Neurology JSC will perform the following functions, some or all of which may be addressed directly at any given Neurology JSC meeting:

(a) maintain the list of Collaboration Targets and the High Interest Target List, as such lists may be updated from time to time in accordance with this Agreement, and attach such lists to the minutes of the next meeting of the Neurology JSC following any update to the High Interest Target List or Collaboration Targets;

(b) review and provide advice on the Collaboration Program Research Plan for each Collaboration Program, and the Development Plan for each Development Candidate;

(c) review the overall progress of Isis' efforts to achieve Target Sanction with respect to each Collaboration Program that has not achieved Target Sanction status;

(d) review the overall progress of Isis' efforts to discover, identify, optimize and select the Development Candidate for each Collaboration Program;

(e) amend each Collaboration Program Research Plan for each Collaboration Program, and the Development Plan for each Development Candidate upon unanimous agreement;

(f) review and provide advice on the Phase 1 Trial Design and the PoC Trial Design for each Collaboration Program; and

(g) such other review and advisory responsibilities as may be assigned to the Neurology JSC pursuant to this Agreement.

1.11.3. **Decision Making**. Isis will give due consideration to, and consider in good faith, the recommendations and advice of the Neurology JSC regarding the conduct of the Collaboration Program. Subject to Section 1.5.1 and Section 1.5.2(a), prior to Option exercise, Isis will have the final decision-making authority regarding [***] and [***]. After Option exercise for a particular Collaboration Program, Biogen Idec will have the final decision-making authority regarding the Manufacture, Development and Commercialization of Products for such Collaboration Program. Except as otherwise permitted by Section 1.5.2(a) and Section 1.11.2(e), the Neurology JSC will have no decision

making authority and will act as a forum for sharing information about the activities conducted by the Parties hereunder and as an advisory body, in each case only on the matters described in, and to the extent set forth in, this Agreement.

1.11.4. **Term of the Neurology JSC**. Isis' obligation to participate in the Neurology JSC, or any of its subcommittees, will terminate upon Biogen Idec's exercise (or expiration) of the Option for the last Collaboration Program. Thereafter, Isis will have the right, but not the obligation, to participate in Neurology JSC meetings upon Isis' request.

1.11.5. **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager under this Agreement (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the Neurology JSC and performing the activities listed in SCHEDULE 1.11.5.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. **Exclusivity; Right of First Negotiation**.

2.1.1. **Exclusivity Covenants**.

(a) **Isis' Exclusivity Covenants During the Drug Discovery Term for High Interest Targets**. On a High Interest Target-by-High Interest Target basis, Isis agrees that, except in the performance of its obligations under this Agreement and except as set forth in Section 2.3, Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, it will not work for

the benefit of any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes such High Interest Target in the Field from the Effective Date until the date on which the High Interest Target List is dissolved in accordance with Section 1.3.1(d).

(b) **The Parties' Exclusivity Covenants During the Option Period for Collaboration Targets**. On a Collaboration Target-by-Collaboration Target basis, each Party agrees that, except in the performance of its obligations under this Agreement and except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, it will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field from the Effective Date through the expiration or earlier termination of the applicable Option Period.

(c) **Isis' Exclusivity Covenant After Option Exercise**. On a Collaboration Target-by-Collaboration Target basis, except as set forth in Section 2.1.2, Section 2.1.3, Section 10.4.2 or Section 10.4.3, if Biogen Idec timely exercises the Option in accordance with this Agreement, then Isis will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***]; and

(ii) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***].

(d) **Biogen Idec's Exclusivity Covenant After Option Exercise**. After Option exercise, Biogen Idec's exclusivity obligations under Section 2.1.1(b) will be extended and will continue for so long as and to the extent of [***].

Except as expressly set forth in Section 2.1.2, Section 2.1.3, or Section 10.4.3, in no event will Isis have the right to [***].

2.1.2. **Right of First Negotiation for Follow-On Compounds**. On a Collaboration Program-by-Collaboration Program basis, during the period commencing on the Effective Date and ending upon (i) if the applicable Option is not exercised in accordance with this Agreement, [***], or (ii) if the applicable Option is

exercised in accordance with this Agreement, [***] (such period, the "***ROFN Period***"), Isis hereby grants to Biogen Idec a right of first negotiation to develop and commercialize any Follow-On Compound developed by or on behalf of Isis, which right of first negotiation is granted on the following terms and conditions:

(a) Within [***], Biogen Idec may provide Isis with a non-binding, good faith written notice expressing Biogen Idec's desire for Isis to identify a Follow-On Compound (a "***Follow-On Interest Notice***"). If (i) Biogen Idec does not, within such [***] period, provide Isis with a Follow-On Interest Notice, or (ii) Biogen Idec does timely provide Isis with a Follow-On Interest Notice but the Parties do not agree on a [***] related to such Follow-On Compound by 5:00 pm (Eastern Time) on the [***] following the date of Option exercise, then, Isis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development and manufacture of a Follow-On Compound; *provided, however*, that during the ROFN Period, Isis will not grant any license (or an option to obtain such a license) under any intellectual property owned, controlled or licensed by Isis to make, use or sell any Follow-On Compound (a "***Follow-On Agreement***") *unless and until* Isis provides a written notice to Biogen Idec (a "***Follow-On Negotiation Notice***"), which notice identifies [***]. Isis will not initiate

negotiations regarding or enter into such a Follow-On Agreement with any Third Party until [***] (each, a "***ROFN Termination Event***").

(b) If Biogen Idec or one of its Affiliates responds within [***] after its receipt of the Follow-On Negotiation Notice indicating that Biogen Idec or one of its Affiliates desires to negotiate with Isis regarding the proposed Follow-On Agreement, Isis and Biogen Idec or one of its Affiliates will negotiate in good faith with each other until the [***] after the date Isis provided Biogen Idec the Follow-On Negotiation Notice (or such other period as mutually agreed by the Parties) (the "***Negotiation Period***") regarding a mutually satisfactory Follow-On Agreement (which may take the form of an amendment to this Agreement). During the Negotiation Period, Isis will make at least [***] to Biogen Idec or its Affiliate setting forth all material business and legal terms on which Isis would be willing to enter into the proposed Follow-On Agreement with Isis; *provided, that* neither Party will have any obligation to enter into a Follow-On Agreement. If the Negotiation Period expires before Biogen Idec or its Affiliate and Isis have entered into such a Follow-On Agreement, Isis will have no further obligation to negotiate with Biogen Idec or its Affiliates with respect to such Follow-On Agreement and Isis will be free to negotiate and enter an agreement with a Third Party with respect to a Follow-On Agreement [***]; *provided, however*, that Isis will not enter into any such Follow-On Agreement with any Third Party unless the terms and pricing of such Follow-On Agreement, [***] during the Negotiation Period. If, with

respect to any Follow-On Compound that was the subject of the Follow-On Agreement previously discussed by the Parties, after the end of the Negotiation Period and prior to Isis entering into a Follow-On Agreement with a Third Party, [***] regarding the Follow-On Compound, Isis' obligations and Biogen Idec's rights under Section 2.1.2(a) and this Section 2.1.2(b) will reset and Isis will provide Biogen Idec with a new Follow-On Negotiation Notice.

(c) Any Follow-On Agreement entered into by Isis with a Third Party in accordance with Section 2.1.2(b) will be a Permitted License to the extent related to the Follow-On Compound.

(d) Notwithstanding anything to the contrary in this Agreement, until [***], Isis will provide to Biogen Idec a Follow-On Negotiation Notice for each [***] pursuant to this Section 2.1.2, *unless* Isis enters into a Follow-On Agreement with a Third Party pursuant to this Section 2.1.2 and the terms of such agreement do not permit Isis to grant Biogen Idec rights with respect to the applicable Follow-On Compound.

2.1.3. **Limitations and Exceptions to Isis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Isis' practice of the following will not violate Section 2.1.1 or Section 2.1.2:

(a) Any activities pursuant to the Prior Agreements as in effect on the Effective Date; and

(b) The granting of, or performance of obligations under, Permitted Licenses.

2.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target in the Field with the intent of treating a neurological or neuromuscular disease. Isis and Biogen Idec are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes a gene that is *not* a Collaboration Target (or with respect to Isis, that is *not* a High Interest Target, to the extent Section 2.1.1(a) still applies) for any indication, even if such products are designed to treat a neurological or neuromuscular disease.

2.3. **Consequences of Isis-Discovered High Interest Target Development Candidate.** Isis may work for itself (but not for the benefit of a Third Party) to conduct drug discovery activities to identify a High Interest Target Development Candidate, including drug screening, identification, characterization, optimization, and, subject to Section 1.5.6, research collaborations with academic or non-profit institutions. Isis will notify the Neurology JSC of any such activities and keep the Neurology JSC reasonably apprised of the status thereof. If Isis designates a High Interest Target Development Candidate targeting a particular High Interest Target (such target, an ***"Accelerated Target"***), Isis

may notify Biogen Idec in writing regarding Isis' designation of such High Interest Target Development Candidate and will provide Biogen Idec the applicable High Interest Target Development Candidate Data Package; *provided however* that, unless otherwise agreed to by Biogen Idec in writing, Isis may not provide Biogen Idec more than one such High Interest Target Development Candidate Data Package in any rolling [***] month period. Within [***] following Biogen Idec's receipt of the applicable High Interest Target Development Candidate Data Package, Biogen Idec may (i) if Biogen Idec has not designated all three Collaboration Targets, designate the Accelerated Target as a Collaboration Target, or (ii) if Biogen Idec has designated all three Collaboration Targets, substitute-out a Collaboration Target in exchange for substituting-in the Accelerated Target as a Collaboration Target (pursuant to the procedures set forth in Section 1.4.2). If Biogen Idec does not, within such [***] period, designate the Accelerated Target as a Collaboration Target pursuant to clause (i) or (ii) of this Section 2.3, then, such Accelerated Target will no longer be a High Interest Target and Isis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Accelerated Target.

ARTICLE 3.
EXCLUSIVE OPTION

3.1. **Option**.

3.1.1. **Advance Data Disclosure**. On or about 90 days before the date on which Isis estimates that the database will be locked for the first PoC Trial for a particular Collaboration Program (each an "***Estimated Lock Date***"), Isis will provide Biogen Idec with a written notice of such Estimated Lock Date. If Biogen Idec provides written notice to Isis [***] after Biogen Idec's receipt of the notice regarding the Estimated

Lock Date that Biogen Idec has a good faith intention to exercise the Option for the applicable Collaboration Program under Section 3.1.3, then as soon as reasonably practicable after Isis receives such notice from Biogen Idec, Isis will provide Biogen Idec with an early preview of the information to be included in the [***] for the applicable Collaboration Program to the extent then in Isis' possession and not already provided to Biogen Idec, to assist Biogen Idec with its decision of whether to exercise the Option. Within 15 Business Days after Biogen Idec's receipt of such data, Biogen Idec will provide Isis with a [***] notice of whether Biogen Idec still intends to exercise the Option for the applicable Collaboration Program, *provided, however*, that Biogen Idec's failure to do so will not be deemed a breach of this Agreement.

3.1.2. **PoC Trial Completion Notice**. On a Collaboration Program-by-Collaboration Program basis, Isis will provide to Biogen Idec or its designated Affiliate (i) a copy of the most recent Investigator's Brochure for the applicable Product, (ii) written notice from Isis regarding completion of the first PoC Trial, and (iii) the PoC Data Package for such Collaboration Program, to the extent not already provided to Biogen Idec under Section 3.1.1 above (such notice and package, a

"***PoC Trial Completion Notice***") promptly, and in any event within 30 days after database lock for the PoC Trial for such Collaboration Program. Within 15 days of receipt of the PoC Trial Completion Notice, Biogen Idec or an Affiliate will notify Isis of any omissions or deficiencies that Biogen Idec or its Affiliate believes in good faith cause the PoC Trial Notice to be incomplete ("***Deficiency Notice***"). Isis will promptly, and in any event within 15 days of receipt of the Deficiency Notice, resubmit a complete PoC Trial Completion Notice to Biogen Idec or its designated Affiliate, including any information required to be included in the PoC Data Package that Biogen Idec identified in the Deficiency Notice. If the Parties do not agree as to whether the PoC Trial Completion Notice is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete PoC Trial Completion Notice.

3.1.3. **Option and Option Deadline**. On a Collaboration Program-by-Collaboration Program basis, Isis hereby grants to Biogen Idec and its Affiliates an exclusive option to obtain the license set forth in Section 4.1.1 with respect to such Collaboration Program (each an "***Option***"). Each Option will be available to Biogen Idec and its Affiliates until 5:00 pm (Eastern Time) on the [***] following Biogen Idec's receipt of a complete PoC Trial Completion Notice for the applicable Collaboration Program (the "***Option Deadline***"); *provided, however*, if Biogen Idec determines that an HSR Filing is required to be made under the HSR Act to exercise the Option and notifies Isis of such determination within [***] after Biogen Idec's receipt of the complete PoC Trial Completion Notice, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the Option Deadline will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date. If, by the Option Deadline, Biogen Idec or its designated Affiliate (i) notifies Isis in writing that it wishes to exercise the applicable Option, and (ii) pays to Isis the license fee set forth in Section 6.3, Isis will, and hereby does, grant to Biogen Idec or its designated Affiliate the license set forth in Section 4.1.1. If, by the Option Deadline, Biogen Idec or its designated Affiliate has not both (y) provided Isis a written notice stating that Biogen Idec is exercising its Option, and (z) paid Isis the license fee in accordance with Section 6.3, then Biogen Idec's Option for the applicable Collaboration Program will expire.

3.1.4. **HSR Compliance**.

(a) **HSR Filing**. If Biogen Idec notifies Isis pursuant to Section 3.1.3 that an HSR Filing is required to exercise an Option under this Agreement, each of Biogen Idec and Isis will, within five Business Days after such notice from Biogen Idec (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby. The Parties will cooperate with one

another to the extent necessary in the preparation of any such HSR Filing. Each Party will be responsible for its own costs and expenses (other than filing fees, which Biogen Idec will pay) associated with any HSR Filing.

(b) **HSR Clearance**. In furtherance of obtaining HSR Clearance for an HSR Filing filed under Section 3.1.4(a), Isis and Biogen Idec will use their respective commercially reasonable efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority, Biogen Idec and its Affiliates will not be required to (i) sell, divest (including through a license or a reversion of licensed or assigned rights), hold separate, transfer or dispose of any assets, operations, rights, product lines, businesses or interest therein of Biogen Idec or any of its Affiliates (or consent to any of the foregoing actions); or (ii) litigate or otherwise formally oppose any determination (whether judicial or administrative in nature) by a governmental authority seeking to impose any of the restrictions referenced in clause (i) above.

3.2 **Restrictions on Isis' Right to Grant Diagnostic Rights; Right to Negotiate Diagnostic Rights**.

3.2.1 On a Product-by-Product basis, Isis hereby grants to Biogen Idec and its Affiliates an option (the "***Diagnostic Option***") to negotiate during the Full Royalty Period the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen Idec and its Affiliates until the expiration of the [***].

3.2.2 During the [***], Isis (i) has the right to [***], and (ii) will not [***].

3.2.3 If, during the [***], Isis grants any Third Party a [***], then Isis will promptly notify Biogen Idec of such [***] and will offer Biogen Idec a [***].

ARTICLE 4.
LICENSE GRANTS TO BIOGEN IDEC

4.1. License Grants to Biogen Idec.

4.1.1. Development and Commercialization License. Subject to the terms and conditions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, effective upon Biogen Idec's exercise of the Option for a particular Collaboration Program in accordance with this Agreement, Isis grants to Biogen Idec a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to

research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Collaboration Program in the Field.

4.1.2. Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, Biogen Idec will have the right to grant sublicenses under the license granted under Section 4.1.1 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents and Isis Know-How, to an Affiliate of Biogen Idec or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How, solely to (y) [***] or (z) [***];

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within 90 days of first learning of any breach of such sublicense terms, Biogen Idec fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2, which failure would cause an adverse effect on Isis, Biogen Idec hereby grants Isis the right to enforce such sublicense terms on Biogen Idec's behalf and will cooperate with Isis (which cooperation will be at Biogen Idec's sole expense and will include, Biogen Idec joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen Idec will provide Isis with a true and complete copy of any sublicense granted pursuant to this Section 4.1.2 within 30 days after the execution thereof.

(b) In connection with Biogen Idec's selecting and engaging one or more CMOs to supply Clinical Supplies after Option exercise, or supply API and Finished Drug Product for Commercialization, Isis will, at Biogen Idec's option, either (1) grant a license from Isis to [***] under the [***] to the extent necessary for [***], which Isis agrees it will grant to [***], or, (2) permit Biogen Idec to grant a sublicense from Biogen Idec to [***]. Each such manufacturing agreement between Biogen Idec and a CMO will contain [***]. Biogen Idec will provide Isis with a true and complete copy of any manufacturing agreement entered into with a CMO within 30 days after the execution thereof. Notwithstanding the foregoing, if Isis fails to comply with the terms of this Section 4.1.2(b) and does not cure such failure within 90 days after written notice from Biogen Idec specifying the details of any such failure, Biogen Idec will have the right to [***].

(c) Effect of Termination on Sublicenses. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by Biogen Idec; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by Biogen Idec, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Biogen Idec. Biogen Idec agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

4.1.3. No Implied Licenses. All rights in and to Licensed Technology not expressly licensed to Biogen Idec under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to Biogen Idec Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by Biogen Idec or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.4. License Conditions; Limitations. Subject to Section 6.8, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) any applicable Third Party Obligations, (ii) the Prior Agreements, and (iii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Biogen Idec in writing (or via electronic data room) prior to Biogen Idec's exercise of the applicable Option. Isis will disclose to Biogen Idec any Third Party Obligations Isis believes apply to applicable Products each time Isis provides Biogen Idec with (x) the [***]; (y) the [***]; and (z) the [***], and Biogen Idec will have the right to elect to exclude any Third Party Patent Rights and Know-How to which such Third Party Obligations apply by providing Isis written notice prior to Option exercise. If, prior to an Option exercise, Biogen Idec provides Isis with such a written notice to exclude certain Third Party Patent Rights and Know-How, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement. If Biogen Idec does not provide Isis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to an Option exercise, such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to Products) will be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement.

4.1.5. Trademarks for Products. If Biogen Idec exercises an Option hereunder, to the extent that (i) Isis owns any trademark(s) specific to a Product which Isis used prior to the exercise of the Option, and (ii) Biogen Idec reasonably believes such

trademark(s) would be necessary or useful for the marketing and sale of the applicable Product, then upon Biogen Idec's request and at Biogen Idec's sole cost and expense relating to such assignment, Isis will assign its rights and title to such trademark(s) to Biogen Idec or one or more designated Affiliates sufficiently in advance of the First Commercial Sale of the Product to enable Biogen Idec or its Affiliates to offer such Product for sale under such trademark(s). Other than trademarks owned by Isis prior to the exercise of the applicable Option, Biogen Idec or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.4, will be the exclusive owner of, all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products.

4.2. Assignment of Isis Product-Specific Patents; Grant Back to Isis.

4.2.1. After Biogen Idec has obtained the license for a particular Collaboration Program under Section 4.1.1 and following review and consideration by the Joint Patent Committee, Isis will assign to Biogen Idec or one or more of its designated Affiliates, Isis' ownership interest in (i) all Isis Product-Specific Patents related to such Collaboration Program in the Field that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties), and (ii) any Jointly-Owned Program Patents Covering Products related to such Collaboration Program, and thereafter, subject to Section 7.2.4, Isis will have no further right to control any aspect of the Prosecution and Maintenance of such Isis Product Specific Patents and such Jointly-Owned Program Patents. The assignment of Patent Rights assigned in this Section 4.2.1 will occur within 30 days of Biogen Idec obtaining the license under Section 4.1.1.

4.2.2. Biogen Idec grants to Isis a worldwide, exclusive, sublicensable license under any Isis Product Specific Patents and Jointly-Owned Program Patents assigned to Biogen Idec under Section 4.2.1, (i) for all [***], (ii) to conduct activities under other Collaboration Program Research Plans and (iii) to [***] to the extent permitted by this Agreement.

4.3. Ownership of and Assistance with Regulatory Filings. If requested by Biogen Idec, Isis' and Biogen Idec's regulatory teams will meet and begin to prepare a plan, which plan will be complete no later than [***] prior to such anticipated filing date, for drafting and reviewing the sections of the NDA and MAA for the applicable Product (including establishing responsibilities for drafting and reviewing common technical document ("***CTD***") modules, authorship, plan activity timelines and associated costs and expenses) to ensure a smooth transition to Biogen Idec, accelerate CTD completion and facilitate rapid NDA and MAA filing. The Parties will act in good faith and mutually agree upon each such plan, *provided, however*, that, after exercising an Option for the applicable Collaboration Program, Biogen Idec will have final decision making authority with respect to the [***]. Once such plan is complete, each Party will use Commercially Reasonable Efforts to execute their respective tasks and responsibilities under such plan in the time frames set forth in such plan. After exercising an Option for a particular Collaboration Program, if Biogen Idec requests, Isis will assist Biogen Idec in preparing

regulatory filings for the Product, under terms negotiated in good faith between Isis and Biogen Idec, including payment for Isis' time at Isis' then applicable FTE Rate plus any reasonable out of pocket expenses incurred by Isis in providing such assistance.

4.4. Subcontracting. Subject to the terms of this Section 4.4, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

4.5. Technology Transfer after Option Exercise. On a Collaboration Program-by-Collaboration Program basis, Isis will promptly, but no later than [***] after Biogen Idec exercises its Option for such Collaboration Program hereunder, deliver to Biogen Idec or one or more designated Affiliates:

4.5.1. Isis Know-How. All Isis Know-How in Isis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.4.1(b), including transferring the IND for the applicable Development Candidate to Biogen Idec together with all regulatory documentation (including drafts) related to the applicable Development Candidate. To assist with the transfer of such Isis Know-How, Isis will make its personnel reasonably available to Biogen Idec during normal business hours for up to [***] ([***]) of Isis' time for each Collaboration Program to transfer such Isis Know-How under this Section 4.5.1. Thereafter, if requested by Biogen Idec, Isis will provide Biogen Idec with a reasonable level of assistance in connection with such transfer, which Biogen Idec will reimburse Isis for its time incurred in providing such assistance at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in providing such assistance.

4.5.2. Isis Manufacturing and Analytical Know-How. Solely for use by Biogen Idec, its Affiliates or a Third Party acting on Biogen Idec's behalf to Manufacture API in Biogen Idec's own or an Affiliate's manufacturing facility, all Isis Manufacturing and Analytical Know-How in Isis' Control relating to applicable Products, which is necessary for the exercise by Biogen Idec, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1. Upon Biogen Idec's request, subject to Section 4.1.2, Isis will provide up to [***] for [***] ([***]) of its time for each Collaboration Program to transfer such Manufacturing and Analytical Know-How under this Section 4.5.2 to any Third Party Manufacturing API, Clinical Supplies or Finished Drug Product on Biogen Idec's behalf solely to Manufacture API, Clinical Supplies or Finished Drug Product in accordance with the terms of this Agreement. Thereafter, if requested by Biogen Idec, Isis will provide Biogen Idec with a reasonable level of assistance in connection with such transfer, which Biogen Idec will reimburse Isis for its time

incurred in providing such assistance at the then-applicable Isis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Isis in providing such assistance.

4.5.3. **API and Product**. Upon Biogen Idec's written request, Isis will sell to Biogen Idec any bulk API, Clinical Supplies and Finished Drug Product in Isis' possession at the time of Option exercise, at a price equal to [***].

ARTICLE 5.

DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **Biogen Idec Diligence**. Following an Option exercise, Biogen Idec will be solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of applicable Products; and Biogen Idec will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each Collaboration Program for which an Option has been exercised. If Biogen Idec exercises an Option for a Product involving a Collaboration Target added in accordance with Section 1.3.2 that is associated with [***], Biogen Idec will use Commercially Reasonable Efforts to Develop such Product for use in a [***].

5.1.1. **Specific Performance Milestone Events**. Without limiting any of the foregoing, following an Option exercise, Biogen Idec will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.1.1, as such schedule may be updated from time to time in accordance with Section 1.5.2(a) ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in SCHEDULE 5.1.1; *provided, however*, [***].

5.1.2. **Integrated Development Plan**. On a Product-by-Product basis, Biogen Idec will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization (each, an "***Integrated Development Plan***" or "***IDP***"). Biogen Idec will prepare the IDP no later than [***] after Option exercise, and the IDP will contain information consistent with Biogen Idec's Development and Commercialization plans for its similar products at similar stages of development. Once Biogen Idec has prepared such plans, Biogen Idec will update the IDP consistent with Biogen Idec's standard practice and provide such updates to Isis [***]. Biogen Idec and Isis will

meet [***] basis to discuss the draft of the IDP and Biogen Idec will consider, in good faith, any proposals and comments made by Isis for incorporation in the final IDP. Notwithstanding the foregoing, Biogen Idec's obligations to provide Isis with information or reports with respect to a Product under this Section 5.1.2 will terminate if [***].(1)

5.1.3. **Investigator's Brochure**. Upon Option exercise, Isis will provide to Biogen Idec an up-to-date version of the Investigator's Brochure for the applicable Product. After Option Exercise, Biogen Idec will keep Isis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the Investigator's Brochure for each Product to Isis [***] and when Development of such Product results in any substantive change to the safety or risk to the Product. Biogen Idec's obligations under this Section 5.1.3 will terminate with respect to a Product if [***].

5.1.4. **Isis' Participation in Regulatory Meetings**. Biogen Idec will provide Isis with as much advance written notice as practicable of any meetings Biogen Idec has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product or that directly relate to Isis' antisense oligonucleotide chemistry platform, and will allow Isis to participate in any such meetings under the direction of Biogen Idec.

5.1.5. **Regulatory Communications**. Biogen Idec will provide Isis with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of Products for Isis' review and comment, and Biogen Idec will consider in good faith including any comments provided by Isis to such documents and communications.

5.1.6. **Class Generic Claims**. To the extent Biogen Idec intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, Biogen Idec will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis, *provided, however*, that Biogen Idec is not obligated to incorporate such proposals and comments in any such claims and regulatory filings.

5.1.7. **Applicable Laws**. Biogen Idec will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP,

(1) [***].

in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.2. **Global Safety Database; Pharmacovigilance Agreement**.

5.2.1. **Pharmacovigilance Agreement**. As soon as reasonably practicable following designation of a particular Development Candidate, and in any event no later than [***] prior to the date on which Isis anticipates filing an IND for the associated Product with a Regulatory Authority, the Parties will enter into a Safety Drug Exchange Agreement relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with such Product occurring prior to the First Commercial Sale in any country on terms substantially the same as the terms of the Safety Drug Exchange Agreement to be entered into by the Parties with respect to adverse events associated with products developed under the Isis/Biogen Preexisting Development Agreements. No later than 30 days prior the date on which Biogen reasonably anticipates that it will exercise an Option, Biogen Idec will so notify Isis and the pharmacovigilance departments of each of Isis and Biogen Idec will meet and determine the approach to be taken for the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with the applicable Product occurring after such First Commercial Sale, consistent with the provisions of this Section 5.2. Such approach will be documented in a separate and appropriate written pharmacovigilance agreement between the Parties which will control with respect to the subject matter covered therein (the "***Pharmacovigilance Agreement***"). Such agreement will specify that the owner of the IND for a Product will be the global commercial safety database owner for such Product with primary responsibility for maintaining such database, and that Isis will be and remain the owner of the Isis Internal ASO Safety Database with primary responsibility for maintaining such database. Such agreement will also specify that, prior to Biogen Idec's exercise of the applicable Option, Isis will communicate updates on safety data regarding a Product to Biogen Idec through monthly telephone calls between the drug safety representatives of Biogen Idec and Isis. Biogen Idec and Isis will jointly review and discuss safety issues arising under any Collaboration Program that may have implications on any Development Plan for such Collaboration Program. Biogen Idec may suggest actions to address Product safety data or audit findings, and Isis will consider all such suggestions in good faith. The Pharmacovigilance Agreement will be in accordance with, and will enable the Parties and their Affiliates or licensees or Sublicensees, as applicable, to fulfill, local and international regulatory reporting obligations to Regulatory Authorities and other Applicable Law.

5.2.2. **Isis' Antisense Safety Database**.

(a) Isis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Internal ASO Safety Database***"). In an effort to

maximize understanding of the safety profile and pharmacokinetics of Isis compounds, after Biogen Idec exercises an Option, Biogen Idec will cooperate in connection with populating the Isis Internal ASO Safety Database. To the extent collected by Biogen Idec and in the form in which Biogen Idec uses/stores such information for its own purposes, Biogen Idec will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Biogen Idec (but not later than 30 days after Biogen Idec's receipt of such information). In connection with any reported serious adverse event, Biogen Idec will provide Isis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Biogen Idec will provide Isis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within 30 days following the date such information is filed or is available to Biogen Idec, as applicable. Furthermore, Biogen Idec will promptly provide Isis with any supporting data and answer any follow-up questions reasonably requested by Isis. All such information disclosed by Biogen Idec to Isis will be Biogen Idec Confidential Information; *provided*, *however*, that Isis may disclose any such Biogen Idec Confidential Information to (i) Isis' other partners pursuant to Section 5.2.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Isis does not disclose the identity of a Product or Biogen Idec. Biogen Idec will deliver all such information to Isis for the Isis Internal ASO Safety Database to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). Biogen Idec will also cause its Affiliates and Sublicensees to comply with this Section 5.2.2(a).

(b) From time to time, Isis utilizes the information in the Isis Internal ASO Safety Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Isis will promptly (and in no event later than 5 Business Days following identification by Isis) inform Biogen Idec of such issues and, if requested, provide the data supporting Isis' conclusions.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Option Fee**. In partial consideration for Biogen Idec's Options hereunder, within five Business Days following the Effective Date, Biogen Idec will pay Isis an Option fee equal to $10,000,000 for each of the three Collaboration Programs for an aggregate payment of $30,000,000.

6.2. **Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen Idec's Options, on a Collaboration Program-by-Collaboration Program basis, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by a Product under such Collaboration Program:

TABLE 1

Pre-Licensing Milestone Event	Milestone Event Payment
[***]	$ [***]
[***]	[***]

[***]	[***]

On a Collaboration Program-by-Collaboration Program basis, Biogen Idec will pay to Isis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Product under such Collaboration Program, even if Biogen Idec has exercised the applicable Option prior to achievement of the Milestone Event; *provided, however*, that if Biogen Idec exercises the Option prior to achievement of the [***] Milestone Event, then the milestone payment for achievement of the [***] Milestone Event will be [***].

6.3. **License Fee**. On an Option-by-Option basis, together with Biogen Idec's written notice to Isis stating that Biogen Idec is exercising such Option in accordance with this Agreement, Biogen Idec will pay to Isis a license fee of $[***]; *provided, however*, that if Biogen Idec exercises the Option prior to the [***], the license fee for such Option will be [***].

6.4 **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Collaboration Program-by-Collaboration Program basis, Biogen Idec will pay to Isis the milestone payments as set forth in TABLE 2 below when a milestone event (each, a *"**Post-Licensing Milestone Event**"*) listed in TABLE 2 is first achieved by a Product under such Collaboration Program:

TABLE 2

Post-Licensing Milestone Event	Milestone Event Payment
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]
[***]	$ [***]

On a Collaboration Program-by-Collaboration Program basis, if Biogen Idec exercises an Option prior to the [***], Biogen Idec will pay to Isis [***] upon the earlier of (a) [***] or (b) [***]. For the avoidance of doubt, if such $[***] payment is paid pursuant to clause (b) of the preceding sentence, such payment will be in addition to the amount due upon the occurrence of the corresponding Post-Licensing Milestone Event under TABLE 2 above.

Notwithstanding anything to the contrary in this Section 6.4, if Biogen Idec exercises an Option for a Product involving a Collaboration Target added in accordance with Section 1.3.2, and such Product achieves a Post-Licensing Milestone Event, once with respect to a neurological disease or neuromuscular disease, and [***], then Biogen Idec will pay to Isis (i) one hundred percent (100%) of the applicable amount set forth in TABLE 2 above when such Product achieves a Post-Licensing Milestone Event for the first time and (ii) [***] of the applicable amount set forth in TABLE 2 above when such Product achieves a Post-Licensing Milestone Event for the second time.

6.5. **Limitations on Milestone Payments; Exceptions; Notice**.

6.5.1. On a Product-by-Product basis, the $[***] milestone payment is creditable against the first Milestone Event Payment for [***]. For example, if the [***] Milestone Event is achieved by a Product in the [***], then the milestone payment for such Milestone Event is [***] the first to occur of the (i) [***] (ii) [***] or (iii) [***] milestone payments for such Product.

6.5.2. On a Collaboration Program-by-Collaboration Program basis, except as set forth in the second paragraph under TABLE 2 above, each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the Milestone Event regardless of how many Products under such Collaboration Program achieve such Milestone Event.

6.5.3. If a particular Milestone Event is not achieved because Development activities transpired such that achievement of such earlier Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Milestone Event the Milestone Event payment applicable to such earlier Milestone Event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due.

6.5.4. Each time a Milestone Event is achieved under this ARTICLE 6, Biogen Idec will send Isis, or Isis will send Biogen Idec, as the case may be, a written notice

thereof promptly (but no later than [***]) following the date of achievement of such Milestone Event and such payment will be due within [***] of the date such notice was delivered.

6.6. **Royalty Payments to Isis**.

6.6.1. **Biogen Idec Full Royalty**. As partial consideration for the rights granted to Biogen Idec hereunder, subject to the provisions of this Section 6.6.1 and Section 6.6.2, Biogen Idec will pay to Isis royalties on a Collaboration Program-by-Collaboration Program basis, on Annual worldwide Net Sales of Products included in the applicable Collaboration Program sold by Biogen Idec, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 3 below (the "***Biogen Idec Full Royalty***"):

TABLE 3

Royalty Tier	Annual Worldwide Net Sales of Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%

3	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Annual worldwide Net Sales will be calculated by [***].

(a) Biogen Idec will pay Isis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Biogen Idec will provide reports and payments to Isis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Full Royalty Period.

(b) For purposes of clarification, any Isis Product-Specific Patents assigned to Biogen Idec as set forth in Section 4.2.1 will still be considered Isis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.6.2. **Application of Royalty Rates**. All royalties set forth under Section 6.6.1 are subject to the provisions of this Section 6.6.2, and are payable as follows:

(a) **Full Royalty Period**. Biogen Idec's obligation to pay Isis the Biogen Idec Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, if, within the [***], a Generic Product is sold in a country, then the Biogen Idec Full Royalty rate used to pay Isis royalties on such Product in such country will be reduced to [***]% of the otherwise applicable Biogen Idec Full Royalty rate. For the purpose of determining the [***] for a particular Product under this Section 6.6.2(b), if requested by Biogen Idec, Isis and Biogen Idec will meet and confer and mutually agree upon the Parties' best estimate of when the Full Royalty Period [***] in each country where Products are being sold.

(c) **Reduced Royalty Period**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 3 of Section 6.6.1, Biogen Idec will pay Isis royalty rates (the "***Biogen Idec Reduced Royalty***") on Net Sales of Products calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided, however*, that the Biogen Idec Reduced Royalty rate in each country will in no event exceed the [***].

(d) **Limitation on Aggregate Reduction for Biogen Idec Royalties**.

(i) In no event will the aggregate royalty reductions under Section 6.6.2(b) and Section 6.6.2(c) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than [***] for such Product.

(ii) In no event will the aggregate royalty offsets under Section 6.8.3(b) and Section 6.8.3(d) reduce the royalties payable to Isis on Net Sales of a Product in any given period to an amount that is less than the greater of [***].

For example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is less than [***]%, then the offsets under Section 6.8.3(b) and Section 6.8.3(d) will not apply during such Calendar Year but the full Royalty Quotient reduction pursuant to Section 6.6.2(c) will apply.

As an additional example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is [***]%, and the [***] in such Calendar Year are [***]% of the applicable royalty rates in TABLE 3 of Section 6.6.1, then Biogen Idec may apply the offsets under Section 6.8.3(b) and Section 6.8.3(d) until the actual royalty payment made to Isis in such Calendar Year is equal to [***]% of the applicable royalty rates in TABLE 3 of Section 6.6.1.

(e) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis, other than [***], Biogen Idec's obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Reduced Royalty Period in such country. "***Reduced Royalty Period***" means, on a country by country basis, the period commencing upon the expiration of the [***] for such Product in such country and ending when the [***].

(f) **Royalty Examples**. SCHEDULE 6.6.2(f) attached hereto contains examples of how royalties will be calculated under this Section 6.6.

(g) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.6.2, different royalty rates apply to Net Sales of Products from different countries, Biogen Idec will [***] such Net Sales [***]. SCHEDULE 6.6.2(g) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

6.7. **Reverse Royalty Payments to Biogen Idec for a Discontinued Product**.

6.7.1. **Reverse Royalty for a Discontinued Product**. If Isis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Biogen Idec has paid Isis the license fee under Section 6.3, then following the First Commercial Sale of such Discontinued Product by Isis or its Affiliates or Sublicensees, Isis will pay Biogen Idec or its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Isis' obligation to pay Biogen Idec Reverse Royalties will [***].

6.7.2. **Applicable Royalty Provisions**. In addition to this Section 6.7, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 6 governing payment of royalties from Biogen Idec to Isis will govern the payment of Reverse Royalties from Isis to Biogen Idec under this Section 6.7, *mutatis mutandis*, including the provisions of Sections 6.6.2, 6.8, 6.9, 6.10, 6.11, and 6.12.

6.8. **Third Party Payment Obligations**.

6.8.1. **Existing Isis In-License Agreements**.

(a) Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to Biogen Idec under Section 4.1.1 were in-licensed or were acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.8.1 or in a separate written agreement between the Parties (all such license or purchase agreements being the "***Isis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development and Commercialization of a Product by Biogen Idec under this Agreement.

(b) Any payment obligations arising under the Isis In-License Agreements as existing on the Effective Date as they apply to Products will be paid by [***] as [***].

6.8.2. **New In-Licensed Isis Product-Specific Patents; Isis Manufacturing and Analytical Patents**. If after the Effective Date, Isis obtains Third Party Patent Rights necessary or useful to Develop, Manufacture or Commercialize a Product that would have been considered an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license granted to Biogen Idec under Section 4.1.1 if Biogen Idec agrees in writing to pay Isis as [***].

6.8.3. **Additional Core IP In-License Agreements**.

(a) Biogen Idec will promptly provide Isis written notice of any Additional Core IP Biogen Idec believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to Biogen Idec under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify Biogen Idec, and Biogen Idec may obtain such a Third Party license and, subject to Section 6.6.2(d)(ii), Biogen Idec may offset an amount equal to [***]% of any [***] paid by Biogen Idec under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If it is unclear whether certain intellectual property identified by Biogen Idec pursuant to Section 6.8.3(a) is Additional Core IP under Section 6.8.3(b), Isis will send written notice to such effect to Biogen Idec, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether Biogen Idec is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.8.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(d) Notwithstanding the determination of the Third Party lawyer under Section 6.8.3(c), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen Idec asserting that [***], Biogen Idec will be permitted to [***].

6.8.4. **Other Third Party Payments**.

(a) **Isis' Third Party Agreements**. Except as otherwise expressly agreed to by Biogen Idec under clause (iii) of Section 1.3.2 or Section 6.8.2, after Option exercise, Biogen Idec will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Isis where either [***].

(b) **Biogen Idec's Third Party Agreements**. Without limiting any applicable [***] under Section 6.8.3(b), Biogen Idec will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Biogen Idec as they apply to Products.

6.9. **Payments**.

6.9.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Biogen Idec will make royalty payments to Isis under this Agreement within [***] following the end of each such

Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used. If no royalties are payable in respect of a given Calendar Quarter, Biogen Idec will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, Biogen

Idec will provide Isis a [***] report estimating the total Net Sales of, and royalties payable to Isis for Products projected for such Calendar Quarter.

6.9.2. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable [***], irrevocable and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange calculated by using the foreign exchange rates published in Bloomberg during the applicable month starting two Business Days before the beginning of such month and ending two Business Days before the end of such month as utilized by Biogen Idec, in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout Biogen Idec's operations.

6.9.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Biogen Idec will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by Biogen Idec hereunder.

6.10. **Audits**. After Option exercise, during the Agreement Term and for a period of [***] thereafter, at the request and expense of Isis, Biogen Idec will permit an independent certified public accountant of nationally recognized standing appointed by Isis, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of Biogen Idec, such auditor will sign a nondisclosure agreement reasonably acceptable to Biogen Idec in form and substance. Any and all records of Biogen Idec examined by such independent certified public accountant will be deemed Biogen Idec's Confidential Information. Upon completion of the audit, the accounting firm will provide both Biogen Idec and Isis with a written report disclosing whether the royalty payments made by Biogen Idec are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Biogen Idec, it is shown that Biogen Idec's payments under this Agreement were less than the royalty amount which should have been paid, then Biogen Idec will make all payments required to be made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 6.12. If, as a result of any inspection of the books and records of Biogen Idec, it is shown that Biogen Idec's payments under this Agreement were greater than the royalty amount which should have been paid, then [***]; *provided*, *however*, that if [***]. Isis will pay for such audit, except

that if Biogen Idec is found to have underpaid Isis by more than [***] of the amount that should have been paid, Biogen Idec will reimburse Isis' reasonable costs of the audit.

6.11. **Taxes**.

6.11.1. **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.11.2. **Withholding Tax**. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax withholding or similar obligations in respect of royalties, milestone payments, and other payments made by the paying Party to the receiving Party under this Agreement. To the extent the paying Party is required to deduct and withhold taxes on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

6.11.3. **Tax Cooperation**. Isis will provide Biogen Idec with any and all tax forms that may be reasonably necessary in order for Biogen Idec to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Biogen Idec's timely receipt of such tax forms from Isis, Biogen Idec will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the applicable laws. Isis will provide any such tax forms to Biogen Idec upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by applicable law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.11.

The provisions of this Section 6.11 are to be read in conjunction with the provisions of Section 12.4 below.

6.12. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. Ownership.

7.1.1. Isis Technology and Biogen Idec Technology. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and Biogen Idec will own and retain all of its rights, title and interest in and to the Biogen Idec Know-How and Biogen Idec Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

7.1.2. Agreement Technology. As between the Parties, Biogen Idec is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Biogen Idec or its Affiliates under this Agreement ("***Biogen Idec Program Know-How***") and any Patent Rights that claim or cover Biogen Idec Program Know-How ("***Biogen Idec Program Patents***" and together with the Biogen Idec Program Know-How, the "***Biogen Idec Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Biogen Idec to Isis under this Agreement. As between the Parties, Isis is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Isis or its Affiliates ("***Isis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Isis Program Patents***"), and will retain all of its rights, title and interest thereto, subject to any assignment, rights or licenses expressly granted by Isis to Biogen Idec under this Agreement. Any Know-How discovered, developed, invented or created jointly under this Agreement by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf ("***Jointly-Owned Program Know-How***"), and any Patent Rights that claim or cover such Jointly-Owned Program Know-How ("***Jointly-Owned Program Patents***", and together with the Jointly-Owned Program Know-How, the "***Jointly-Owned Program Technology***"), are owned jointly by Biogen Idec and Isis on an equal and undivided basis, including all rights, title and interest thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Program Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Program Technology. The Biogen Idec Program Patents, Isis Program Patents and Jointly-Owned Program Patents are collectively referred to herein as the "***Program Patents***."

7.1.3. Joint Patent Committee.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this

Agreement, and will cooperate with respect to the activities set forth in this ARTICLE 7. Isis' obligation to participate in the JPC will terminate upon Biogen Idec's exercise of (or the expiration or termination of) the last Option. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. A strategy will be discussed with regard to intellectual property considerations when selecting each Development Candidate, prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents that would be or are licensed to Biogen Idec under Section 4.1.1 in connection with a Product and Biogen Idec Product-Specific Patents, defense against allegations of infringement of Third Party Patent Rights, and licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to designate a Development Candidate or prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) Isis will provide the Joint Patent Committee with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by Isis and a Third Party in the performance of activities under the Collaboration Programs or solely by a Third Party performing activities under the Collaboration Programs on Isis' behalf (such Know-How and Patents, the "***Collaborator IP***") promptly after Isis receives notice or otherwise becomes aware of the existence of such Collaborator IP. The JPC will determine whether any such Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Isis for potential designation as a Development Candidate. If the JPC (or independent patent counsel engaged pursuant to this Section 7.1.3(b)) determines that any Collaborator IP would be infringed by such Development, registration, Manufacture or Commercialization, [***]. In case of a dispute in the Joint Patent Committee over whether any Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Isis for potential designation as the Development Candidate, at Biogen Idec's request, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties, taking into account any existing prior art. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be borne by Biogen Idec.

(c) In addition, the Joint Patent Committee will be responsible for the determination of inventorship of Program Patents in accordance with

United States patent laws. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and Biogen Idec) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such dispute, even after seeking the Neurology JSC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(d) The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this ARTICLE 7. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Executives for input and resolution pursuant to Section 12.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement.

7.2. Prosecution and Maintenance of Patents.

7.2.1. Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for the applicable Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit. On a Collaboration Program-by-Collaboration Program basis, until the earlier of Biogen Idec's exercise of the Option and the expiration or termination of the Option, Isis will use Commercially Reasonable Efforts to diligently Prosecute and Maintain all Isis Product-Specific Patents and any Jointly-Owned Program Patents Covering Products, in each case to the extent that Isis has the right to Prosecute and Maintain such Patent Rights.

7.2.2. Licensed Patents and Biogen Idec Patents.

(a) Licensed Patents In General. Prior to exercise of an Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such Option,

subject to Section 7.2.2(b), Section 7.2.3 and Section 7.2.4. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.

(b) Licensed Patents After Option Exercise. After Isis assigns to Biogen Idec or one or more designated Affiliates Isis' ownership interest in (i) all Isis Product-Specific Patents that are owned (whether solely owned or jointly owned with one or more Third Parties) by Isis, and (ii) any Jointly-Owned Program Patents Covering Products in accordance with Section 4.2, Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of all such Isis Product-Specific Patents and Jointly-Owned Program Patents to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such assignment, subject to Section 7.2.3 and Section 7.2.4, and will grant Isis the license set forth in Section 4.2.2.

(c) Biogen Idec Patents. Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen Idec Patents, subject to Section 7.2.3 and Section 7.2.4.

7.2.3. Jointly-Owned Program Patents. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that do not Cover Products. Prior to exercise of an Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such Option. After exercise of an Option, Biogen Idec will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such Option.

7.2.4. Other Matters Pertaining to Prosecution and Maintenance of Patents.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Isis Core Technology Patents set forth on Schedule 8.2.4(a), together with all Product-Specific Patents or Jointly-Owned Program Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If Biogen Idec elects (a) not to file and prosecute patent applications for the Jointly-Owned Program Patent Rights or Isis Product-Specific Patents that have been licensed or assigned to Biogen Idec under this Agreement or the Biogen Idec Product-Specific Patents ("***Biogen Idec-Prosecuted Patents***") in a particular country, (b) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any Biogen-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the

Biogen Idec-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then Biogen Idec will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and except as set forth in Section 7.2.4(c) Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Biogen Idec-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Biogen Idec will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Biogen-Prosecuted Patent in such country in Isis' own name, but only to the extent that Biogen Idec is not required to take any position with respect to such abandoned Biogen Idec-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by Biogen Idec under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such Biogen Idec-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify Biogen Idec if Isis intends to abandon such Biogen Idec-Prosecuted Patent.

(c) Notwithstanding Section 7.2.4(b) above, if, after having consulted with outside counsel, Biogen Idec reasonably determines that filing or continuing to prosecute a patent application in a particular country for a Biogen Idec Prosecuted Patent (the ***"Conflicting Patent Right"***) is reasonably likely to adversely affect the scope, validity or enforceability of a patent application or issued patent in a particular country for another Biogen Idec Prosecuted Patent (the ***"Superior Patent Right"***), in each case where both the Conflicting Patent Right and the Superior Patent Right if issued would meet the criteria set forth in clause (i) of Section 6.6.2(a), then *so long as* Biogen Idec continues to Prosecute and Maintain the Superior Patent Right in accordance with this Agreement, Isis will not have the right under Section 7.2.4(b) above to file or prosecute the Conflicting Patent Right.

(d) If, during the Agreement Term, Isis intends to abandon any Isis Product-Specific Patent for which Isis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if the applicable Option Deadline has not passed, Isis will notify Biogen Idec of such intention at least 60 days before such Patent Right will become abandoned, and Biogen Idec will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice. Notwithstanding anything to the contrary in this Agreement, if Biogen Idec assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 7.2.4(d), Biogen Idec will have no obligation to notify Isis if Biogen Idec intends to abandon such Isis Product-Specific Patent.

(e) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(f) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 7.2.4(f), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(g) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3. Patent Costs.

7.3.1. Jointly-Owned Program Patents. Unless the Parties agree otherwise, Isis and Biogen Idec will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Program Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Program Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Program Patents.

7.3.2. Licensed Patents and Biogen Idec Patents. Except as set forth in Section 7.2.4 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided, however*, that after Option exercise, Biogen Idec will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Isis Product-Specific Patents.

7.4. Defense of Claims Brought by Third Parties.

7.4.1. If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to Option exercise at its sole cost and expense and (b) Biogen Idec will have the first right, but not the obligation, to defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend

against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within 60 days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense

initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2. **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Biogen Idec will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide Biogen Idec with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.2, and Isis will promptly furnish Biogen Idec with a copy of each communication relating to the alleged infringement received by Isis.

7.4.3. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (*i.e.*, each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5. **Enforcement of Patents Against Competitive Infringement**.

7.5.1. **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a Collaboration Target in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within 10 days.

7.5.2. **Prior to Option Exercise**. For any Competitive Infringement with respect to a Product occurring after the Effective Date but before Option exercise, Isis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and Biogen Idec will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Isis will have the sole right to control such litigation. Isis will provide Biogen Idec with prompt written notice of the commencement of any such Proceeding, and Isis will keep Biogen Idec apprised of the progress of such Proceeding. If Isis fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, which extension will apply only in the event that Isis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Biogen Idec will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided that* Isis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.3. **Following Option Exercise**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Product) occurring after Option exercise, so long as part of such Proceeding Biogen Idec also enforces any Patent Rights Controlled by Biogen Idec (including any Isis Product-Specific Patents assigned by Isis to Biogen Idec under this Agreement) being infringed that Cover the Product, then Biogen Idec will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however*, Biogen Idec will have the right to control such litigation. If Biogen Idec fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, if Biogen Idec has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Biogen Idec will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.3 to the extent involving any Isis Core Technology Patents or Isis Manufacturing and Analytical Patents.

7.5.4. Joinder.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.5, the costs and expenses of each Party incurred pursuant to this Section 7.5.4(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.4, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

7.5.5. Share of Recoveries. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds constituting direct or actual damages for acts of infringement occurring prior to Biogen Idec's exercise of the Option will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after Biogen Idec's exercise of the Option [***]; then

(d) any remaining proceeds constituting punitive or treble damages will be allocated between the Parties as follows: the Party initiating the Proceeding will receive and retain [***]% of such proceeds and the other Party will receive and retain [***]% of such proceeds.

7.5.6. Settlement. Notwithstanding anything to the contrary under this ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

7.5.7. 35 USC 271(e)(2) Infringement. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents that have not been assigned to Biogen Idec under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so

that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

7.6. Other Infringement.

7.6.1. Jointly-Owned Program Patents. With respect to the infringement of a Jointly-Owned Program Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable out-of-pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) any remaining proceeds constituting direct damages will be [***], and (iii) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (A) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***]; and (B) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, such Party will receive [***]% of such proceeds and the other Party will receive [***]% of such proceeds.

7.6.2. Patents Solely Owned by Isis. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

7.6.3. Patents Solely Owned by Biogen Idec. Biogen Idec will retain all rights to pursue an infringement of any Patent Right solely owned by Biogen Idec which is other than a Competitive Infringement and Biogen Idec will retain all recoveries with respect thereto.

7.7. Patent Listing.

7.7.1. Biogen Idec's Obligations. Biogen Idec will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Biogen Idec will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Biogen Idec will retain final decision-making authority as to the listing of all applicable Patent Rights for the Product that are not Isis Core Technology Patents or Isis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Isis' Obligations**. Isis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Isis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, Isis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **CREATE Act**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party will have the right to make an election under the CREATE Act when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, the Parties will use reasonable efforts to cooperate and coordinate their activities with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in the CREATE Act.

7.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) New Third Party License the restrictions and obligations of which Biogen Idec has agreed to under Section 6.8.2, (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Biogen Idec hereunder and, this Agreement purports to grant any such rights to Biogen Idec, Isis will act in such regard with respect to such Patent Rights at Biogen Idec's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

7.11. **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to the Product. After exercising an Option, Biogen Idec will determine which relevant patents will be extended.

7.12. **No Challenge**. As a material inducement for Isis entering into this Agreement, Biogen Idec covenants to Isis that during the Agreement Term, solely with respect to rights to the Licensed Patents that are included in a license granted to Biogen Idec under Section 4.1.1, Biogen Idec, its Affiliates or Sublicensees will not, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other

than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents. For purposes of clarification and without limiting any other available remedies, if Biogen Idec takes any of the actions described in clause (a) or clause (b) of this Section 7.12, Biogen Idec will have materially breached this Agreement and Isis may terminate this Agreement under Section 10.2.4(b).

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

8.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

8.1.1. such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

8.1.2. such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.3. this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid and binding obligation, enforceable against it in accordance with the terms hereof;

8.1.4. the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

8.1.5. no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

8.1.6. it has not employed (and, to the best of its knowledge, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs, provided that such Party may reasonably rely on a representation made by such contractor or consultant) any Person debarred by the FDA (or subject to a similar sanction of EMA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of the Product and its activities under each Collaboration Program.

8.2. **Representations and Warranties of Isis**. Isis hereby represents and warrants to Biogen Idec, as of the Effective Date, that:

8.2.1. To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Biogen Idec under Section 4.1.1 upon the exercise of the Option for a Product arising under the Collaboration Programs) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for Biogen Idec to further Develop and Commercialize a Product.

8.2.2. The Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Isis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize Compounds contemplated under the Collaboration Programs in the Field. Isis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Technology in a manner that conflicts with any rights granted to Biogen Idec hereunder.

8.2.3. Neither Isis nor its Affiliates owns or Controls any Patent Rights or Know How covering formulation or delivery technology as of the Effective Date that would be useful or necessary in order for Biogen Idec to further Develop or Commercialize Compounds contemplated under the Collaboration Programs.

8.2.4. SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) set forth true, correct and complete lists of all Isis Core Technology Patents, and Isis Manufacturing and Analytical Patents that apply to the Compounds contemplated under the Collaboration Programs as of the Effective Date (the ***"Isis Platform Technology"***), respectively, and indicates whether each such Patent Right is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Isis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to Biogen Idec under this Agreement.

8.2.5. There are no claims, judgments or settlements against or owed by Isis or its Affiliates or pending against Isis or, to the best of Isis' knowledge, threatened against Isis, in each case relating to the Isis Platform Technology, Isis

Manufacturing and Analytical Know-How, Isis Know-How, Collaboration Targets or High Interest Targets that could impact activities under this Agreement. To the best of Isis' knowledge, there are no claims, judgments or settlements against or owed by any Third Party that is party to a Prior Agreement, or pending or threatened claims or litigation against any Third Party that is party to a Prior Agreement, in each case relating to the Isis Platform Technology, Isis Manufacturing and Analytical Know-How, Isis Know-How, Collaboration Targets or High Interest Targets that would impact activities under this Agreement.

8.2.6. At the Effective Date (a) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude that any Isis Core Technology Patent or Isis Manufacturing and Analytical Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude the inventorship of each Isis Core Technology Patent or Isis Manufacturing and Analytical Patent is not properly identified on each patent, and (c) all official fees, maintenance fees and annuities for the Isis Core Technology Patent or Isis Manufacturing and Analytical Patent have been paid and all administrative procedures with governmental agencies have been completed.

8.2.7. Isis has set forth on SCHEDULE 6.8.1 or in a separate written agreement with Biogen Idec true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Isis has licensed or acquired the Licensed Technology Controlled by Isis as of the Effective Date licensed to Biogen Idec under Section 4.1.1 that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of any High Interest Target listed on the High Interest Target List as of the Effective Date and any Compounds as contemplated under the Collaboration Program targeting [***]. All Isis In-License Agreements are in full force and effect and have not been modified or amended. Neither Isis nor, to the best knowledge of Isis, the Third Party licensor in an Isis In-License Agreement is in default with respect to a material obligation under such Isis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Isis In-License Agreement.

8.2.8. SCHEDULE 8.2.8 is a complete and accurate list of all agreements that create Third Party Obligations with respect to the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents that affect the rights granted by Isis to Biogen Idec under this Agreement.

8.3. **Isis Covenants**. Isis hereby covenants to Biogen Idec that, except as expressly permitted under this Agreement:

8.3.1. Isis will promptly amend SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) and submit such amended Schedules to Biogen Idec if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical

Patents or Isis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Isis will maintain and not breach any Isis In-License Agreements and any agreements with Third Parties entered into after the Effective Date ("***New Third Party Licenses***") that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or may become subject to a license from Isis to Biogen Idec for the Development Candidate under this Agreement;

8.3.3. Isis will promptly notify Biogen Idec of any material breach by Isis or a Third Party of any New Third Party License, and in the event of a breach by Isis, will permit Biogen Idec to cure such breach on Isis' behalf upon Biogen Idec's request;

8.3.4. Isis will not amend, modify or terminate any Isis In-License Agreement or New Third Party License in a manner that would adversely affect Biogen Idec's rights hereunder without first obtaining Biogen Idec's written consent, which consent may be withheld in Biogen Idec's sole discretion;

8.3.5. Isis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Biogen Idec under this Agreement;

8.3.6. Isis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 2.1;

8.3.7. all employees and contractors of Isis performing Development activities hereunder on behalf of Isis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Isis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. If, after the Effective Date, Isis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Biogen Idec to further Develop, Manufacture or Commercialize a Product, and Biogen Idec has exercised its Option and the license granted to Biogen Idec under this Agreement is in effect, Isis will make such technology available to Biogen Idec on commercially reasonable terms.

8.4. **DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. BIOGEN IDEC AND ISIS UNDERSTAND THAT EACH PRODUCT IS THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT**

NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF EACH PRODUCT.

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1. **Indemnification by Biogen Idec**. Biogen Idec will indemnify, defend and hold harmless Isis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

9.1.1. the gross negligence or willful misconduct of Biogen Idec, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Biogen Idec's performance of its obligations or exercise of its rights under this Agreement;

9.1.2. any breach of any representation or warranty or express covenant made by Biogen Idec under ARTICLE 8 or any other provision under this Agreement;

9.1.3. the Development or Manufacturing activities that are conducted by or on behalf of Biogen Idec or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Isis pursuant to this Agreement); or

9.1.4. the Commercialization of a Product by or on behalf of Biogen Idec or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Isis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance for which Isis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Isis**. Isis will indemnify, defend and hold harmless Biogen Idec and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

9.2.1. the gross negligence or willful misconduct of Isis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Isis' performance of its obligations or exercise of its rights under this Agreement;

9.2.2. any breach of any representation or warranty or express covenant made by Isis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Biogen Idec pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees with respect to a Discontinued Product.

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Biogen Idec or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Biogen Idec has an indemnity obligation pursuant to Section 9.1.

9.3. **Procedure**. If a Person entitled to indemnification under Section 9.1 or Section 9.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will (i) inform the indemnifying Party in writing of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle such Claim at the sole discretion of the indemnifying Party, *provided that* (A) such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party and (B) the indemnifying Party first obtain the written consent of the Indemnitee with respect to such settlement, which consent will not be unreasonably withheld), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any Losses with respect to the Claim. The provisions of Section 7.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 9.1 or Section 9.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4. **Insurance**.

9.4.1. **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, *provided*, *that*, at a minimum, Isis will maintain, in force from 30 days prior to enrollment of the first patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate. Isis will furnish to Biogen Idec evidence of such insurance upon request.

9.4.2. **Biogen Idec's Insurance Obligations**. Biogen Idec will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, *provided*, *that*, at a minimum, Biogen Idec will maintain, in force from 30 days prior to enrollment of the first patient in a Clinical

Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate and, *provided further* that such coverage is increased to at least $[***] at least 30 days before Biogen Idec initiates the First Commercial Sale of a Product hereunder. Biogen Idec will furnish to Isis evidence of such insurance upon request. Notwithstanding the foregoing, Biogen Idec may self-insure to the extent that it self-insures for its other products, but at a minimum will self-insure at levels that are consistent with levels customarily maintained against similar risks by similar companies in Biogen Idec's industry.

9.5. **LIMITATION OF CONSEQUENTIAL DAMAGES**. **EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.3(a) BY BIOGEN IDEC OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 10.
TERM; TERMINATION

10.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to all Products (or Discontinued Product(s)) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to all Products (or Discontinued Products) in all countries pursuant to Section 10.1.1; and

10.1.3. where every Option has expired as a result of Biogen Idec not providing Isis a written notice stating Biogen Idec is exercising such Options and paying Isis the

applicable license fees under Section 6.3 by the Option Deadline, or as a result of Section 1.5.2(d) or Section 10.4.2.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***."

10.2. Termination of the Agreement.

10.2.1. Biogen Idec's Termination for Convenience. At any time following payment by Biogen Idec of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Biogen Idec will be entitled to terminate this Agreement as a whole, or terminate this Agreement in part with respect to a particular Collaboration Program, for convenience by providing 90 days written notice to Isis of such termination.

10.2.2. Termination for Failure to Divest Directly Competitive Product. If a Competing Acquirer does not, during the Divestiture Period, divest itself of a Directly Competitive Product related to a Collaboration Program, terminate the development and commercialization of such Directly Competitive Product or assign this Agreement to a Third Party that is not itself developing or commercializing such a Directly Competitive Product as set forth in Section 12.5, Biogen Idec may terminate this Agreement solely with respect to the Collaboration Program affected by the Directly Competitive Product immediately upon providing written notice to Isis.

10.2.3. Termination Due to Failure to Obtain HSR Clearance.

(a) If the Parties make an HSR Filing with respect to a Collaboration Program under Section 3.1.4 of this Agreement and the HSR Clearance Date has not occurred on or prior to 90 days after the effective date of the latest HSR Filing made by the Parties, this Agreement will terminate solely with respect to such Collaboration Program (i) at the election of either Party immediately upon notice to the other Party, if the FTC or the DOJ has instituted (or threatened to institute) any action, suit or proceeding including seeking, threatening to seek or obtaining a preliminary injunction under the HSR Act against Biogen Idec and Isis to enjoin or otherwise prohibit the transactions contemplated by this Agreement related to such Collaboration Program, or (ii) at the election of either Party, immediately upon notice to the other Party, if the Parties have not resolved any and all objections of the FTC and DOJ as contemplated by Section 3.1.4(b). Notwithstanding the foregoing, this Section 10.2.3 will not apply if an HSR Filing is not required to fully perform this Agreement with respect to a Collaboration Program.

(b) If this Agreement is terminated with respect to a Collaboration Program in accordance with Section 10.2.3(a), then, *until* [***] as follows:

(i) If Isis [***]; and

(ii) If Isis, its Affiliates or the licensee [***].

Nothing in this Section 10.2.3(b) obligates Isis to (y) [***] or (z) [***].

10.2.4. Termination for Material Breach.

(a) **Biogen Idec's Right to Terminate**. If Biogen Idec believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.5.3, which is governed by Section 10.2.5 below), then Biogen Idec may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, Biogen Idec may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice to Isis. Without limiting the foregoing, breach by a Party of ARTICLE 2 of this Agreement constitutes a material breach of this Agreement with respect to the Collaboration Program affected by such breach. Notwithstanding the foregoing, if Biogen Idec is entitled to terminate this Agreement under this Section 10.2.4(a) with respect to a breach by Isis that negatively and materially impacts the value of a particular Collaboration Program, in lieu of such termination (and as its sole and exclusive remedy for such breach), Biogen Idec may elect to substitute another High Interest Target for the applicable Collaboration Target by sending Isis a written notice within 60 days of Biogen Idec becoming aware of such breach, in which case, such substitution will not be counted for purposes of determining whether Biogen Idec has exceeded the Substitution Limit.

(b) **Isis' Right to Terminate**. If Isis believes that Biogen Idec is in material breach of (i) a payment obligation under ARTICLE 6, (ii) Section 7.12, or (iii) one or more material provisions of this Agreement where such material breaches have occurred multiple times over the course of at least a 12-month period (where such material breach is not a single continuous event) demonstrating a pattern of failing to timely comply with Biogen Idec's obligations under this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 5.1, which is governed by Section 10.2.5 below), then Isis may deliver notice of such material breach to Biogen Idec. If the breach is curable, Biogen Idec will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If Biogen Idec fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis in its sole discretion may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice thereof to Biogen Idec.

10.2.5. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis, in Biogen Idec's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.5.3 prior to Option exercise with respect to a particular Collaboration Program, Biogen Idec will notify Isis and, within 30 days thereafter, Isis and Biogen Idec will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in Section 1.5.3. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by Section 1.5.3 with respect to such Collaboration Program, then subject to Section 10.2.6 below, Biogen Idec will have the right, at its sole

discretion, to (i) terminate this Agreement as it relates to the applicable Collaboration Program or, (ii) prior to Option exercise, Biogen Idec may elect to trigger the alternative remedy provisions of Section 10.3 below as it relates to the applicable Collaboration Program in lieu of terminating this Agreement for such Collaboration Program by providing written notice to Isis. This Section 10.2.5(a) sets forth Biogen Idec's sole and exclusive remedies if Isis fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.5.3 prior to Option exercise.

(b) If Biogen Idec, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 with respect to a Collaboration Program above, Isis will notify Biogen Idec and, within 30 days thereafter, Isis and Biogen Idec will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Biogen Idec's use of Commercially Reasonable Efforts in Section 5.1. Following such a meeting, if Biogen Idec fails to use Commercially Reasonable Efforts with respect to the applicable Collaboration Program as contemplated by Section 5.1, then subject to Section 10.2.6 below, Isis will have the right, at its sole discretion, to terminate this Agreement as it relates to such Collaboration Program.

10.2.6. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.4 or Section 10.2.5 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such 60 day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.4 or Section 10.2.5, or trigger the substitution right under Section 10.2.4(a) or the alternative remedy provisions of Section 10.2.5, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will

remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.7. Termination for Insolvency.

(a) Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

(b) All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "***Bankruptcy Code***") licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, will be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects in writing to continue, and continues, to perform all of its obligations under this Agreement.

10.3. Alternative Remedies to Termination Available to Biogen Idec Prior to Option Exercise. If, prior to Option exercise, with respect to a particular Collaboration Program Biogen Idec elects to (i) exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement for such Collaboration Program by providing written notice of such election to Isis in accordance with Section 10.2.5(a), or (ii) exercise the Option in accordance with [***], then, in each case, *solely with respect to the Collaboration Program giving rise to Biogen Idec's exercise of these alternative remedy provisions*, this Agreement will continue in full force and effect with the following modifications:

(a) Isis will have no further rights or obligations to Develop the Product under the applicable Collaboration Program or participate in the Neurology JSC, JPC or any other subcommittees or working groups established pursuant to this Agreement. Biogen Idec will solely make all decisions that this Agreement would otherwise require or permit the Neurology JSC, JPC or any other subcommittees or working groups, or

the Parties collectively, to make; *provided, however*, that Biogen Idec will not have the right to create any obligations or incur any liabilities for or on behalf of Isis;

(b) effective as of the date of Biogen Idec's notice to Isis electing the alternative remedy provisions of this Section 10.3, Biogen Idec will be deemed for all purposes of this Agreement to have exercised the applicable Option;

(c) Biogen Idec will have and Isis grants, the exclusive license granted to Biogen Idec under Section 4.1.1 for the applicable Collaboration Program;

(d) Biogen Idec may exclude Isis from all discussions with Regulatory Authorities regarding the applicable Products, except to the extent Isis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(e) Biogen Idec's obligation to make further disclosures of Know-How or other information to Isis regarding the applicable Products pursuant to this Agreement (including pursuant to Section 4.5 and Section 5.2.2) will terminate, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement;

(f) Isis will perform its obligations under Section 4.5 with respect to the applicable Product within 60 days of Biogen Idec electing to exercise its alternative remedies under this Section 10.3 or exercising the Option in accordance with [***], and will provide to Biogen Idec and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen Idec in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner; and

(g) the financial provisions of ARTICLE 6 will be modified as follows:

(i) [***] *Payments*. Biogen Idec will [***]; and

(ii) *License Fee*. The license fee set forth in Section 6.3 for the applicable Product will be [***]. Such [***] will be due within 90 days after [***] and Biogen Idec's [***].

The milestone provisions of Section 6.4 and the royalty provisions of Section 6.6 will [***].

10.4. Consequences of Expiration or Termination of the Agreement.

10.4.1. In General. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 at any time and for any reason, the following terms will apply to any Collaboration Program that is the subject of such expiration or termination:

(a) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information, except to the extent such Confidential Information is necessary or useful to conduct activities under a surviving Collaboration Program. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(b) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen Idec has exercised its Option for a particular Collaboration Program, then upon expiration of the Reduced Royalty Period in all countries in which the applicable Products are being or have been sold, Isis will and hereby does grant to Biogen Idec a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Isis Know-How to Manufacture, Develop and Commercialize any Product under such Collaboration Program.

(c) **Accrued Rights**. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(d) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 4.1.2(c) (Effect of Termination on Sublicenses), Section 4.2.2, Section 4.5 (Technology Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.3), Section 6.7 (Reverse Royalty Payments to Biogen Idec for a Discontinued Product), Section 6.9.3 (Records Retention), Section 6.10 (Audits), Section 7.1.1 (Isis Technology and Biogen Idec Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.3(b), Section 10.2.7 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.4 (Remedies Available to Biogen Idec for Isis' Material Breach After Option Exercise)), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and

APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2. Termination Before Option Exercise. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Option exercise, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to each Collaboration Program that is the subject of such expiration or termination:

(a) Biogen Idec's Option under Section 3.1 will expire and Isis will be free to Develop and Commercialize the applicable Product (and any other applicable Compounds) on its own or with a Third Party.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Collaboration Program(s).

(c) To the extent requested by Isis, Biogen Idec will promptly (1) assign to Isis any manufacturing agreements with a CMO identified by Isis to which Biogen Idec is a party, solely to the extent such manufacturing agreements relate to the terminated Collaboration Program and (2) transfer to Isis all data, results and information (including Biogen Idec's Confidential Information and any regulatory documentation (including drafts)) related to the testing and Clinical Studies under the terminated

Collaboration Program(s) in the possession of Biogen Idec and its contractors to the extent such data, results and information were generated by or on behalf of Biogen Idec under this Agreement; and Isis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen Idec's FTE Cost in transferring such data, results and information.

(d) If Biogen Idec terminates this Agreement for convenience with respect to a Collaboration Program after the 30th day following Biogen Idec's receipt of the Development Candidate Data Package for such Collaboration Program, but prior to Option exercise for such Collaboration Program, then Biogen Idec will [***].

(e) Except as explicitly set forth in Section 10.4.1(a), Section 10.4.1(c) or Section 10.4.1(d), Biogen Idec will have no further rights and Isis will have no further obligations with respect to each terminated Collaboration Program.

10.4.3. Termination After Option Exercise. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Option exercise, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any Collaboration Program that is the subject of such termination:

(a) The applicable licenses granted by Isis to Biogen Idec under this Agreement will terminate and Biogen Idec, its Affiliates and Sublicensees will cease selling the applicable Products.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Collaboration Program(s).

(c) Except as explicitly set forth in Section 10.4.1(a), Biogen Idec will have no further rights and Isis will have no further obligations with respect to the terminated Collaboration Program.

(d) If (i) Biogen Idec terminates the Agreement under Section 10.2.1 (Biogen Idec's Termination for Convenience) or (ii) Isis terminates this Agreement under Section 10.2.4(b) (Isis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply *solely with respect to the terminated Collaboration Program(s)*:

(i) Biogen Idec will grant to Isis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Idec Technology Controlled by Biogen Idec as of the date of such reversion that Covers the applicable Discontinued Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Product(s) in the Field (such license will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Biogen Idec will assign back to Isis any Product-Specific Patent Rights that relate to the applicable Discontinued Product(s) previously assigned by Isis to Biogen Idec under this Agreement;

(iii) Biogen Idec will transfer to Isis for use with respect to the Development and Commercialization of the applicable Discontinued Product(s), any Know-How data, results, regulatory information, filings, and files in the possession of Biogen Idec as of the date of such reversion to the extent related to such Discontinued Product(s), and any other information or material specified in Section 4.5;

(iv) Biogen Idec will license to Isis any trademarks that are specific to a Discontinued Product(s) solely for use with such Discontinued Product(s), in accordance with Section 4.1.5, *mutatis mutandis*; *provided, however*, that in no event will Biogen Idec have any obligation to license to Isis any trademarks used by Biogen Idec both in connection with the Product and in connection with the sale

of any other product or service, including any BIOGEN- or BIOGEN IDEC-formative marks;

(v) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Collaboration Program, and Biogen Idec will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in Biogen Idec's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided, however*, if Isis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Isis will notify Biogen Idec of such intention at least 60 days before such Patent Right will become abandoned, and Biogen Idec will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense with counsel of its own choice; and

(vi) Isis will have the obligation to pay royalties to Biogen Idec under Section 6.7 with respect to the applicable Discontinued Product(s). Such payments will be governed by the financial provisions in Section 6.9, and the definition of Net Sales will apply to sales of Discontinued Product(s) by Isis, in each case *mutatis mutandis*.

(e) If Isis terminates this Agreement due to Biogen Idec's material breach or Biogen Idec terminates this Agreement for convenience, upon Isis' written request pursuant to a mutually agreed supply agreement, Biogen will sell to Isis any bulk API, Clinical Supplies and Finished Drug Product in Biogen Idec's possession at the time of such termination, at a price equal to [***].

(f) To the extent requested by Isis, Biogen Idec will promptly assign to Isis any manufacturing agreements solely to the extent related to the applicable Discontinued Products and identified by Isis to which Biogen Idec is a party.

10.4.4. Remedies Available to Biogen Idec for Isis' Material Breach After Option Exercise.

(a) **Termination of Committees and Information Sharing**. If, after Option exercise, Isis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.2.4(a), and Biogen Idec does not wish to terminate this Agreement in its entirety (an "***Isis Breach Event***"), then, in addition to any other remedies Biogen Idec may have under this Agreement or otherwise, Biogen Idec will have the right to do any or all of the following in

Biogen Idec's discretion *solely with respect to the Collaboration Programs that are the subject of the Isis Breach Event*:

(i) Terminate Isis' right to participate in the Neurology JSC, JPC and any other subcommittees or working groups established pursuant to this Agreement;

(ii) Terminate Isis' participation in any ongoing research and development programs under the applicable Collaboration Program and Biogen Idec's funding obligations associated therewith;

(iii) Solely make all decisions required or permitted to be made by such committees or the Parties collectively under this Agreement in connection with the Development and Commercialization of the applicable Product; *provided, however*, that Biogen Idec will not have the right to create any obligations or incur any liabilities for or on behalf of Isis;

(iv) Exclude Isis from all discussions with Regulatory Authorities regarding applicable Products, *except* to the extent Isis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(v) Terminate Biogen Idec's obligation to make further disclosures of Know-How or other information to Isis pursuant to this Agreement related to the applicable Products, including pursuant to Section 4.5 and Section 5.2.2, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Isis to perform its obligations under this Agreement; and

(vi) If Isis has not completed the Development activities that are its responsibility under the applicable Collaboration Program Research Plan and Development Plan, then Biogen Idec may, but will not be obligated to, assume all responsibility for all such Development activities that would have otherwise been Isis' responsibility under this Agreement.

Isis will cooperate with the foregoing and provide to Biogen Idec and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen Idec in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner.

(b) **Biogen Idec's Right of Setoff**. If there is [***] and Biogen Idec does not wish to [***], then, in addition to any other remedies Biogen Idec may have under this Agreement or otherwise, Biogen Idec may setoff against any amounts owed to Isis pursuant to ARTICLE 6 (Financial

Provisions) *solely* with respect to the Collaboration Program that is the subject of the Isis Breach Event [***] (the "***Setoff Amount***"). If Biogen Idec exercises its setoff right under this Section 10.4.4(b), Biogen Idec will provide Isis with a written certificate, signed by Biogen Idec's Chief Financial Officer, certifying that the amount setoff by Biogen Idec represents [***]. Notwithstanding the foregoing, if Isis notifies Biogen Idec in writing (a "***Setoff Dispute Notice***") that it disputes Biogen Idec's assertion that Isis is in material breach of this Agreement or the amount setoff by Biogen Idec (a "***Setoff Dispute***"), then (i) both Parties will participate in the dispute resolution process set forth on SCHEDULE 10.4.4(b), and (ii) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the Advisory Panel of the proper amount that Biogen Idec may setoff (if any) in accordance with SCHEDULE 10.4.4(b), Biogen Idec will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with SCHEDULE 10.4.4(b) the Advisory Panel will determine (1) the amount (if any) that Biogen Idec may setoff against future payments *solely* with respect to the Collaboration Program that is the subject of the Isis Breach Event to Isis going forward, and (2) whether any portion of the escrow account should be released to Isis or returned to Biogen Idec, *provided* that any decision or determination by the Advisory Panel (a "***Panel Decision***") will not be treated as an arbitral award but will be binding on the Parties until and unless a court of competent jurisdiction (the "***Trial Court***") has determined in a judgment regarding some or all of the issues decided in the Panel Decision, and in any Action contemplated by the next sentence hereof the Trial Court will determine the facts and the law *de novo*, and will give a Panel Decision only such persuasive effect, if any, that after review of all of the facts and the law presented to the Trial Court by the Parties, the Trial Court deems appropriate, *provided*, that the Escrow Agent will comply with a Panel Decision that determines that any portion of the escrow account should be released to Isis or returned to Biogen Idec. If it is determined in a judgment by the Trial Court that Isis owes Biogen Idec any damages, then, during the pendency of any appeal of the Trial Court's decision (or, if the Trial Court's decision is not appealed, until Biogen Idec recoups such amount), Biogen Idec may setoff against any future payments *solely* with respect to the Collaboration Programs that are the subject of the Isis Breach Event to Isis under this Agreement the amount of any such damages not paid by Isis. If it is determined in a Trial Court that Biogen Idec has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Biogen Idec as a result of Isis' breach of this Agreement, then Biogen Idec will promptly pay Isis the amount of such excess, plus interest on such amount as provided for in Section 6.12 (Interest on Late Payments), with interest accruing from the time Biogen Idec applied such excess setoff. If, with respect to a

Setoff Dispute, Isis provides a Setoff Dispute Notice to Biogen Idec and Biogen Idec fails to do any of the following: (X) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.4.4(b); (Y) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.4(b); or (Z) pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank, then Biogen Idec will forfeit its right to set off under this Section 10.4.4(b) and SCHEDULE 10.4.4(b) with respect to any and all Setoff Disputes.

ARTICLE 11.
CONFIDENTIALITY

11.1. **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

11.2. **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Isis and Biogen Idec on February 28, 2011 (including any and all amendments thereto). All information exchanged between the Parties under such Confidential Disclosure Agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 11.

11.3. **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided*, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock

exchange); *provided*, *however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) as mutually agreed to in writing by the Parties.

11.4. **Press Release; Publications; Disclosure of Agreement**.

11.4.1. **Public Announcements**. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld, conditioned or delayed.

11.4.2. **Use of Name**. Except as set forth in Section 11.4.9, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.4.3. **Notice of Significant Events**. Each party will immediately notify (and provide as much advance notice as possible, but at a minimum two Business Days advance notice to) the other Party of any event materially related to a Product (including in such notice any disclosure of starting/stopping of a Clinical Study, clinical data or results, material regulatory discussions, filings, Approval or Biogen Idec's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.4. **Prior to Option Exercise**. Prior to Option exercise with respect to a Product, such Product is the sole property of Isis, and Isis will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public; *provided*, that with respect to any proposed press release or other similar public communication by Isis disclosing regulatory discussions, the efficacy or safety data or clinical results related to such Product, (i) Isis will submit such proposed communication to Biogen Idec for review at least two Business Days in advance of such proposed public disclosure, (ii) Biogen Idec will have the right to review and recommend changes to such

communication, and (iii) Isis will in good faith consider any changes that are timely recommended by Biogen Idec.

11.4.5. **After Option Exercise**. After Option exercise with respect to a Product, Biogen Idec will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public; *provided*, that with respect to any proposed press release or other similar public communication by Biogen Idec disclosing regulatory discussions, the efficacy or safety data or results related to such Product or Biogen Idec's sales projections, (i) Biogen Idec will submit such proposed communication to Isis for review at least two Business Days in advance of such proposed public disclosure, (ii) Isis will have the right to review and recommend changes to such communication, and (iii) Biogen Idec will in good faith consider any changes that are timely recommended by Isis.

11.4.6. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Isis or Biogen Idec for a Product, the Parties acknowledge that scientific lead time is a key element of the value of the Products under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 45 days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Collaboration Programs. If, during such 45 day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 45 day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

11.4.7 **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.4.8 **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.4.9 **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or a Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Isis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: ISIS, BIIB). Isis may include the Product (and identify Biogen Idec as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. **Dispute Resolution**.

12.1.1. **Escalation**. In the event of any Dispute (other than a Setoff Dispute, which Setoff Dispute will be resolved pursuant to Section 12.1.3, or dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 12.2), either Party may, within 30 days after either Party notifies the other Party that the Dispute has not been resolved (*provided, that* such notice cannot be given less than 30 days after the Dispute has arisen), make a written request that the Dispute be referred for resolution to the Executive Vice President, Business Development of Biogen Idec and the Chief Operating Officer of Isis (the "***Executives***"). Within 60 days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. Each Party may elect to have such Party's Neurology JSC representatives participate in such meeting, if desired, provided that it provides the other Party with reasonable advance notice of such intent so as to enable the other Party to have its Neurology JSC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such 60 day period, then the Dispute will be referred to mediation under Section 12.1.2.

12.1.2. **Mediation**. If a Dispute subject to Section 12.1.1 cannot be resolved pursuant to Section 12.1.1, or if neither Party timely makes the written request that the Dispute be referred to the Executives, the Parties will resolve any such Dispute in accordance with the dispute resolution procedures set forth in SCHEDULE 12.1.2.

12.1.3. **Setoff Disputes**. Setoff Disputes will be resolved in accordance with Section 10.4.4(b) and SCHEDULE 10.4.4(b).

12.2. **Governing Law; Jurisdiction; Venue; Service of Process**.

12.2.1. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.2.2. Subject to the provisions of Section 12.1, each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court for the District of Delaware (or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Court of Chancery of the State of Delaware, or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Superior Court of the State of Delaware, with respect to the Dispute) for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "***Action***") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named courts, that venue in the above-named courts is improper, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named courts should be dismissed on grounds of forum non conveniens, should be transferred or removed to any court other than the above-named courts, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named courts, or that this Agreement or the subject matter hereof may not be enforced in or by such courts and (c) hereby agrees not to commence any such Action other than before the above-named courts. Notwithstanding the previous sentence, a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

12.2.3. Each Party hereby agrees that service of process: (a) made in any manner permitted by Delaware law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.7, will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. Neither Party will be entitled to recover any Losses relating to any matter

arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.8.3(c)). Except for the offsets and credits explicitly set forth in Section 6.10, Section 6.8.3(b), Section 6.8.3(d) and Section 10.4.4(b), neither Party will have the right to setoff any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.4. **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided*, if Biogen Idec transfers or assigns this Agreement to [***] described in this Agreement, then Biogen Idec (or such Affiliate), will [***] due Isis under ARTICLE 6 for the [***] such that Isis receives [***] assignment. In addition, Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Biogen Idec's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

The [***].

To the extent Isis utilizes a [***] in any year, Isis will [***] to Biogen Idec [***]. To assist Biogen Idec in determining when a refund is due from Isis pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which Biogen Idec [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Isis utilizes a [***], Isis will provide Biogen Idec with Isis' Annual tax returns (federal and state) and, in years in which Isis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. **Change of Control**. On a Product-by-Product basis, if, at any time during the Option Period, a Change of Control occurs involving Isis and a Person that, at the time of the consummation of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Product within the Field or, at any time after such consummation of the Change of Control, develops or acquires a Directly Competitive Product (such Person being hereinafter referred to as a "***Competing Acquirer***") and such Competing Acquirer has not, within [***] of either consummation of the Change of Control in the event the Directly Competitive Product is being developed in human clinical trials or commercialized as of such consummation date or otherwise within [***] of the date of first development or acquisition of such Directly Competitive Product (the "***Divestiture Period***") divested itself of the Directly Competitive Product, terminated development and commercialization of such Directly Competitive Product or assigned this Agreement pursuant to Section 12.4 to a Third Party

that is not itself developing or commercializing a Directly Competitive Product, then (i) Isis will provide written notice to Biogen Idec of the closing of such Change of Control or Divestiture Period, as applicable, (ii) [***] and (iii) and, solely with respect to the Product affected by such Directly Competitive Product, Biogen Idec will have the right, within [***] following such written notice, to either:

(a) if unexercised, exercise the applicable Option by notifying Isis in writing of Biogen Idec's election to license the Product at a prorated license fee payment as compared to the license fee payment set forth in Section 6.3, based upon the stage of Development of the applicable Product at the time of Change of Control or Divestiture Period, as applicable, which license fee payments are set forth on SCHEDULE 12.5 hereto. If Biogen Idec exercises the applicable Option pursuant to this Section 12.5, Biogen Idec will

not be obligated [***]. Upon Biogen Idec's exercise of its Option pursuant to this Section 12.5(a), Biogen Idec will be deemed to have obtained and Isis will be deemed to have granted the license set forth in Section 4.1.1; or

(b) Allow such [***] period to lapse without providing any such notice of election under this Section 12.5, or otherwise provide Isis with written notice within such period electing not to exercise the applicable Option pursuant to Section 12.5(a) above, in either of which cases Isis and Biogen Idec will continue to exercise their rights and perform their respective obligations with respect to the Product under the terms of this Agreement.

Upon Biogen Idec's exercise of an Option pursuant to Section 12.5(a) above, Isis will carry out its technology transfer obligations pursuant to Section 4.5 with respect to the Product. For the avoidance of doubt, except as set forth in this Section 12.5, all other terms and conditions of this Agreement will apply to any such license granted pursuant to Biogen Idec's exercise of its rights hereunder.

12.6. **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the

extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.7. **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: 760-918-3592

with a copy to:
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: 760-268-4922

If to Biogen Idec, addressed to:
Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142
Attention: Richard Brudnick
Fax: 866-795-0181

with a copy to:
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
Attention: Marc A. Rubenstein, Esq.
Fax: 617-235-0706

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service.

12.8. **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States

origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.9. **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a

similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.10. **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

12.11. **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersedes and terminates all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

12.12. **Independent Contractors**. Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party and neither Party will represent that it has such authority.

12.13. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word "including" (in its various forms) means "including without limitation," (c) the words "shall" and "will" have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, "$" is in reference to United

States dollars, and (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.14. **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard), consistently applied.

12.15. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.16. **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.17. **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules and Appendices hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

12.18. **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

12.19. **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

BIOGEN IDEC MA INC.

By: */s/ George Scangos*
Name: George Scangos
Title: Chief Executive Officer

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: Chief Operating Officer and
Chief Financial Officer

SIGNATURE PAGE TO NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

List of Appendices and Schedules

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Accelerated Target***" has the meaning set forth in Section 2.3.

"***Acceptance***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by Biogen Idec of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such MAA

by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by Biogen Idec of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Action***" has the meaning set forth in Section 12.2.2.

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Additional Plan Costs***" means [***].

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. For clarity, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Isis for the purposes of this Agreement under any circumstances.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager***" has the meaning set forth in Section 1.11.5.

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMA in the EU).

"***Annual***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means, with respect to a Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing or reimbursement authorizations necessary for the general marketing and sale of such Product in the marketplace, Approval will not be deemed to have occurred if the final approval to market and sell such Product is being withheld because Biogen Idec (or its Affiliate or Sublicensee) and the Regulatory Authority have not yet determined pricing or reimbursement even if all other approvals, licenses, registrations or authorizations necessary for marketing, sale or use of such Product in such jurisdiction have been obtained. "Approval" does not include authorization by a Regulatory Authority to conduct named patient, compassionate use or other similar activities.

"***ASO***" means a single-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***Audit Report***" has the meaning set forth in Section 6.10.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.7(b).

"***Biogen Idec***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Idec's FTE Cost***" means the FTE Rate applicable to Biogen Idec, *multiplied* by the applicable number of FTEs.

"***Biogen Idec Full Royalty***" has the meaning set forth in Section 6.6.1.

"***Biogen Idec Know-How***" means any Know-How owned, used, developed by, or licensed to Biogen Idec or its Affiliates, in each case to the extent Controlled by Biogen Idec or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Biogen Idec Program Know-How.

"***Biogen Idec Patents***" means any Patent Rights included in the Biogen Idec Technology.

"***Biogen Idec Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Biogen Idec or its Affiliates, in each case to the extent Controlled by Biogen Idec or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Biogen Idec Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec Program Patents***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec Program Technology***" has the meaning set forth in Section 7.1.2.

"***Biogen Idec-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***Biogen Idec Reduced Royalty***" has the meaning set forth in Section 6.6.2(c).

"***Biogen Idec Supported Pass-Through Costs***" means [***].

"***Biogen Idec Technology***" means the Biogen Idec Program Technology, Jointly-Owned Program Technology, Biogen Idec Product-Specific Patents and any trademarks described in Section 4.1.5, owned, used, developed by, or licensed to Biogen Idec or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Biogen-Initiated Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the applicable Development Plan for a Product that are requested by either Party after the Parties have set the initial Cost Estimates for such Development Plan under Section 1.5.2(b), and (i) required by a Regulatory Authority or (ii) agreed to be paid for by Biogen Idec.

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"***Calendar Quarter***" means a period of three consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2012, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.7.4.

"***cGMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Change of Control***" means, with respect to a Party, (a) a merger or consolidation of such Party with a Third Party which results in the voting securities of such Party outstanding immediately prior thereto ceasing to represent at least 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of 50% or more of the combined voting power of the outstanding securities of such Party, (c) the sale or other transfer to a Third Party of all or substantially all of such Party's business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of such Party will approve a plan of complete liquidation of such Party or an agreement for the sale or disposition by such Party of all or a substantial portion of such Party's assets, other than pursuant to the transaction as described above or to an Affiliate. Notwithstanding the foregoing, the sale or issuance of shares in exchange for cash for purposes of a *bona fide* financing will not constitute a Change of Control.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Phase 3 Trial or Phase 4 Trial, or such other study in humans that is conducted in accordance with good clinical

practices and is designed to generate data in support or maintenance of an NDA, MAA or other similar marketing application.

"***Clinical Supplies***" means API and finished drug Product for use in a Clinical Study.

"***CMO***" means a Third Party contract manufacturer Manufacturing API, Clinical Supplies or Finished Drug Product for any purpose under this Agreement.

"***Collaboration Program***" has the meaning set forth in Section 1.2.

"***Collaboration Program Research Plan***" has the meaning set forth in Section 1.5.1(b).

"***Collaboration Target***" means a gene target designated as a Collaboration Target pursuant to Section 1.4.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(b).

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for such Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting such Product in each country.

"***Commercializing Party***" means (a) Biogen Idec, with respect to a Product that is being Developed and Commercialized by or on behalf of Biogen Idec, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of Approval and other relevant

scientific, technical and commercial factors. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to Biogen Idec's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the "*General Activities*" described in SCHEDULE 5.1.1, and Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in each Collaboration Program Research Plan and Development Plan.

"***Competing Acquirer***" has the meaning set forth in Section 12.5.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Compound***" means on a Collaboration Program-by-Collaboration Program basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such

ASO is discovered by Isis prior to or in the performance of the Collaboration Program Research Plan, including each Development Candidate under such Collaboration Program.

"***Confidential Information***" has the meaning set forth in Section 11.1. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(d) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Conflicting Patent Right***" has the meaning set forth in Section 7.2.4(c).

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided*, *however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than Biogen Idec Supported Pass-Through Costs in the case of Biogen Idec), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cost Estimate***" has the meaning set forth in Section 1.5.2(b).

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***CTD***" has the meaning set forth in Section 4.3.

"***Deficiency Notice***" has the meaning set forth in Section 3.1.2.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of the Product to seek Approval for additional indications for the Product.

"Development Candidate" means a Compound that is reasonably determined by Isis' RMC in accordance with Isis' standard procedures for designating development candidates [***] as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 2.

"***Development Candidate Data Package***" means, with respect to a [***], the [***]; *provided* such package contains the [***]. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 2.

"***Development Plan***" has the meaning set forth in Section 1.5.2(a).

"***Diagnostic Option***" has the meaning set forth in Section 3.2.1.

"***Directly Competitive Product***" means with respect to a Product, any product, other than such Product, that is designed to bind to the RNA that encodes the Collaboration Target targeted by such Product.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"Dispositive Disagreement Condition" has the meaning set forth in Section 1.3.2.

"***Dispute***" means any dispute arising between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement that cannot be resolved by the Parties.

"***Divestiture Period***" has the meaning set forth in Section 12.5.

"***DOJ***" has the meaning set forth in Section 3.1.4(a).

"***Drug Development Program***" means the aggregate drug development activities related to each Development Candidate through completion of the first Phase 2 PoC Trial under a Collaboration Program in accordance with the applicable Development Plan for all Collaboration Programs under this Agreement.

"***Drug Discovery Program***" means the aggregate drug discovery activities including drug screening, identification, characterization, optimization and other necessary activities according

to the applicable Collaboration Program Research Plans to achieve Target Sanction status, and then identify a Development Candidate for all Collaboration Programs under this Agreement.

"***Drug Discovery Term***" has the meaning set forth in Section 1.7.1.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***Estimated Lock Date***" has the meaning set forth in Section 3.1.1.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Excluded Payments***" means (i) royalty or profit sharing payments, or any other type of payment based on periodic sales of a Product; (ii) payments made in consideration of Isis' or Isis' Affiliate's equity or debt securities at fair market value; (iii) payments made to pay for or reimburse Isis or Isis' Affiliate for the fully-burdened cost of research and development; (iv) payments made to pay for or reimburse Isis or Isis' Affiliate for the cost of prosecuting, maintaining or defending Patent Rights; and (v) payments made to Isis or Isis' Affiliate to pass-through to a Third Party in satisfaction of a payment obligation Isis or Isis' Affiliate has to such Third Party.

"***Executives***" has the meaning set forth in Section 12.1.1.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means, except as may be limited under Section 4.1.4, the prophylactic or therapeutic use or form of administration of a Product for any indication.

"***Finished Drug Product***" means any drug product containing API as an active ingredient in finished bulk form for the Development or Commercialization by a Party under this Agreement.

"***First Commercial Sale***" means with respect to a Product, the first sale of such Product by Biogen Idec, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of the Product has been obtained in such country.

"***Follow-On Agreement***" has the meaning set forth in Section 2.1.2.

"***Follow-On Compound***" means, with respect to a given Compound for a given Collaboration Target, any ASO (other than the Development Candidate for such Collaboration Target) that is designed to bind to the RNA that encodes such Collaboration Target discovered by or on behalf of Isis following exercise of the applicable Option by Biogen Idec.

"***Follow-On Interest Notice***" has the meaning set forth in Section 2.1.2(a).

"***Follow-On Negotiation Notice***" has the meaning set forth in Section 2.1.2.

"***FTC***" has the meaning set forth in Section 3.1.4(a).

"***FTE***" means a total of 47 weeks or 1880 hours per year of work on the Development, Manufacturing or Commercialization of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Rate***" means $[***] for the Calendar Year 2012. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.6.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Isis as determined using the methodology set forth in SCHEDULE 4.5.3 fairly applied and as employed on a consistent basis throughout Isis' operations.

"***Generic Product***" means, with respect to a particular Product, one or more Third Party product(s) (i) having the same active pharmaceutical ingredient as such Product and for which in the U.S. an ANDA has been filed naming such Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Product has been asserted, and (ii) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus such Product taken in the aggregate, as provided by IMS) during the applicable Calendar Quarter in such country of at least [***]%.

"***GLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

"***High Interest Target***" has the meaning set forth in Section 1.3.1. For clarity, at any given time, if a gene target is not on the High Interest Target List at such time, then such gene target is not a High Interest Target.

"High Interest Target Development Candidate" means an ASO that is discovered by or on behalf of Isis and designed to bind to the RNA that encodes a High Interest Target that is reasonably determined by Isis' RMC to be a development candidate in accordance with Isis' standard procedures for designating development candidates.

"***High Interest Target List***" has the meaning set forth in Section 1.3.1.

"***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***HSR Clearance***" means all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Biogen Idec and Isis with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"***HSR Termination Royalty***" has the meaning set forth in Section 10.2.3(b)(ii).

"***Incremental Tax Cost***" has the meaning set forth in Section 12.4.

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Initiation***" or "***Initiate***" means, with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study and, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 5.1.2.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis/Biogen Preexisting Development Agreements***" means the SMN Agreement and the DMPK Research, Development, Option and License Agreement between the parties dated June 27, 2012.

"***Isis Breach Event***" has the meaning set forth in Section 10.4.4(a).

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(a) attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.8.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.2.

"***Isis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Isis Program Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Jointly-Owned Program Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Jointly-Owned Program Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Isis

Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Platform Technology***" has the meaning set forth in Section 8.2.4.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(c) attached hereto.

"***Isis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Isis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Isis Supported Pass-Through Costs***" means [***].

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Product in Japan.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 7.1.3(a).

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 7.1.2.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents and Isis' interest in Jointly-Owned Program Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Program Patents.

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.5, to the extent necessary or useful to Develop, register, Manufacture or Commercialize such Product.

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means, with respect to a particular Product, a marketing authorization application filed with the EMA after completion of Clinical Studies to obtain Approval for such Product under the

centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means, with respect to a particular Product, the Approval of an MAA by the EMA for such Product in any country in the EU.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy and Spain.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Milestone Event***" means a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***Negotiation Period***" has the meaning set forth in Section 2.1.2.

"***Net Sales***" means the gross amount billed or invoiced on sales of a Product by Biogen Idec, its Affiliates and Sublicensees, less the following: (a) customary trade, quantity, or cash discounts to non-affiliated brokers or agents to the extent actually allowed and taken; (b) amounts repaid or credited by reason of rejection or return; (c) to the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges levied on the production, sale, transportation, delivery, or use of such Product which is paid by or on behalf of Isis; and (d) outbound transportation costs prepaid or allowed and costs of insurance in transit.

In any transfers of a Product between Biogen Idec, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of such Product to an independent Third Party. If Biogen Idec, its Affiliate or a Sublicensee receives non-monetary consideration for a Product, Net Sales are calculated based on the fair market value of that consideration. If Biogen Idec, its Affiliates or Sublicensees uses or disposes of a Product in the provision of a commercial service, the Product is sold and the Net Sales are calculated based on the sales price of the Product to an independent Third Party during the same royalty period or, in the absence of sales, on the fair market value of the Product as determined by the Parties in good faith. Net Sales shall not include any transfers of supplies of the applicable Product for (i) use in clinical trials, pre-clinical studies or other research or development activities, or (ii) a *bona fide* charitable purpose; or (iii) a commercially reasonable sampling program.

"***Neurology JSC***" has the meaning set forth in Section 1.11.1.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Non-Neurological Indications***" means therapeutic uses that are not designed to treat neurological diseases or neuromuscular diseases.

"***Option***" has the meaning set forth in Section 3.1.3.

"Option Acceleration Deadline" has the meaning set forth in Section 1.5.2(d).

"Option Acceleration Notice" has the meaning set forth in Section 1.5.2(d).

"***Option Deadline***" has the meaning set forth in Section 3.1.3.

"***Option Period***" means, with respect to a Collaboration Program, the period beginning on the Effective Date and ending on the expiration or earlier termination of the Option with respect to such Collaboration Program.

"Other Pre-Option Activities" has the meaning set forth in Section 1.8.

"Other Pre-Option Costs" has the meaning set forth in Section 1.8.

"***Panel Decision***" has the meaning set forth in Section 10.4.4(b).

"***Party***" or "***Parties***" means Biogen Idec and Isis individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research.

"***Person***" will mean any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 5.2.1.

"***Phase 1 Trial***" means the first clinical study in human beings Initiated by Isis under the applicable Development Plan pursuant to an IND that has been filed with a Regulatory Authority in a Major Market or Canada. If Biogen Idec exercises the Option before Isis Initiates such a

Phase 1 Trial, then the definition of "*Phase 1 Trial*" means the first clinical study of the applicable Development Candidate in human beings Initiated by Biogen Idec, its Affiliate or its Sublicensee.

"***Phase 1 Trial Design***" means, with respect to a Collaboration Program, the Phase 1 Trial design set forth in the applicable Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JSC).

"***Phase 2 Trial***" means, with respect to a Collaboration Program, a Clinical Study that is intended to explore the feasibility, safety, dose ranging or efficacy of such product, that is prospectively designed to generate sufficient data (if successful) to commence a Phase 3 Clinical Trial (or foreign equivalent) of such product, as further defined in 21 C.F.R. 312.21(b) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 3 Trial***" means , with respect to a Product, a pivotal Clinical Study in humans performed to gain evidence with statistical significance of the efficacy of such product in a target population, and to obtain expanded evidence of safety for such product that is needed to evaluate the overall benefit-risk relationship of such product, to form the basis for approval of an NDA by a Regulatory Authority and to provide an adequate basis for physician labeling, as described in 21 C.F.R. 312.21(c), as amended from time to time, or the corresponding regulation in jurisdictions other than the United States.

"***Phase 4 Trial***" means, with respect to a Product, (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval for such Product or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which such Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

"***PoC Data Package***" means, with respect to a Product, [***], (iv) copies of all filings submitted to Regulatory Authorities regarding such Product, (v) a summary of the patent status relating to such Product, and (vi) a summary of any Third Party Obligations Isis believes relate to the Product.

"***PoC Trial***" means, with respect to a Collaboration Program, the first phase 2a Clinical Study in human patients with a pharmacokinetic or target reduction endpoint or other therapeutic or physiological endpoint.

"***PoC Trial Completion Notice***" has the meaning set forth in Section 3.1.2.

"***PoC Trial Design***" means the PoC Trial design set forth in each Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JSC).

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of a Product, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of such Product and whether such Product has a desired effect.

"***Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.2.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.8 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, on a Collaboration Program-by-Collaboration Program basis, a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date, including any Program Patents, claiming (i) the specific composition of matter of a Product, or (ii) methods of using a Product as a prophylactic or therapeutic; *provided however*, Patent Rights Controlled by Isis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs in general, or (z) include an ASO, the sequence of which targets the RNA that encodes a Collaboration Target and the RNA of a gene that does not encode a Collaboration Target, will not be considered Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Isis Core Technology Patents.

"***Program Patents***" has the meaning set forth in Section 7.1.2.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.6.2(e).

"***Regulatory Approval***" means the approval necessary for the commercial manufacture, distribution, marketing, promotion, offer for sale, use, import, export, and sale of a pharmaceutical product in a jurisdiction regulated by a Regulatory Authority.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"***Replacement Limit***" has the meaning set forth in Section 1.3.3.

"***Research***" means conducting the research activities with Compounds as set forth in each Collaboration Program Research Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***Reverse Royalties***" has the meaning set forth in Section 6.7.1.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***ROFN Period***" has the meaning set forth in Section 2.1.2.

"***ROFN Termination Event***" has the meaning set forth in Section 2.1.2.

"***Royalty Quotient***" has the meaning set forth in Section 6.6.2(c).

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under the applicable Development Plan.

"***Setoff Amount***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.4(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.4(b).

"***SMN Agreement***" means the Development, Option and License Agreement between the Parties dated January 3, 2012.

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.1.1.

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or Biogen Idec Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Subsequent Deal***" has the meaning set forth in Section 10.2.3(b)(i).

"***Substitution Limit***" has the meaning set forth in Section 1.4.2.

"***Superior Patent Right***" has the meaning set forth in Section 7.2.4(c).

"***Target Sanction***" means when the therapeutic potential of a Collaboration Target has been demonstrated in pre-clinical disease models and such Collaboration Target has received approval by Isis' RMC to expend resources to identify a human Development Candidate, all in accordance with Isis' standard processes.

[***]

"***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between Isis and a Third Party (including the Isis In-License Agreements) that relate to a Product, a Collaboration Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Trial Court***" has the meaning set forth in Section 10.4.4(b).

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than seven years, not including in calculating such seven-year period of time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than seven years will not be considered to

have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

Development Candidate Checklist

[***]

SCHEDULE 1.11.1

NEUROLOGY JSC GOVERNANCE

(a) The Neurology JSC will determine the Neurology JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The Neurology JSC will codify these operating procedures in the written minutes of the first meeting.

(b) The Neurology JSC may hold meetings in person or by audio or video conference as determined by the Neurology JSC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at Biogen Idec's facilities in the U.S.). Alliance Managers will attend Neurology JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend Neurology JSC meetings, including any subject matter expert(s) with valuable knowledge of Collaboration Targets or the diseases associated with such Collaboration Targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JSC meetings occur, Neurology JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.11.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The Neurology JSC members from the same Party will collectively have one vote. The Neurology JSC will strive to make recommendations with approval of both Isis members and Biogen Idec members, and record such recommendations in the minutes of the applicable Neurology JSC meeting.

(e) The Neurology JSC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the Neurology JSC dissolves.

SCHEDULE 1.11.5

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Collaboration Programs;

(c) Organizing Neurology JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the Neurology JSC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) Preparing status and progress reports on the above as determined necessary by the Neurology JSC;

(f) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.2;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4; and

(h) Understanding and communicating the components contained in the relationship-management document provided by Isis to Biogen Idec, to assist Biogen Idec in understanding and complying with the contractual obligations under the Isis In-License Agreements after Option exercise.

SCHEDULE 4.5.3

Isis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

100

SCHEDULE 5.1.1

Biogen Idec's Development and Commercialization Activities

[***]

101

SCHEDULE 6.6.2(f)
Royalty Calculation Examples

[***]

102

SCHEDULE 6.6.2(g)

Allocation of Net Sales

[***]

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SCHEDULE 6.8.1

Certain Isis In-License Agreements

(Relevant to the Collaboration Programs and High Interest Targets as of the Effective Date)

[***]

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SCHEDULE 8.2.4(a)

Isis Core Technology Patents

[***]

105

SCHEDULE 8.2.4(b)

Isis Manufacturing and Analytical Patents

[***]

106

SCHEDULE 8.2.4(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Prior Agreements

[***]

SCHEDULE 10.4.4(b)

Advisory Panel Regarding Setoff Disputes

[***]

SCHEDULE 12.1.2

Mediation

1. Mediation.

1.1. If a Dispute cannot be resolved pursuant to Section 12.1.1 of the Agreement (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by the American Arbitration Association (the "***AAA***") in accordance with its Commercial Mediation Procedures then in effect (the "***Procedures***"), as modified by this Section 1.1 of this SCHEDULE 12.1.2. The mediation will be conducted by a single mediator appointed by agreement of the Parties, within 15 days after either Party notifies the other Party of its intention to mediate such Dispute, or failing such agreement, appointed by the AAA in accordance with the Procedures; *provided*, that in either case the mediator will be a retired Delaware state or federal judge. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Dover, Delaware. The Parties agree that they will share equally the costs and expenses of the mediation; *provided*, that each Party will bear its own attorneys' fees and associated costs and expenses. The mediation conference will be held within 30 days after appointment of the mediator, and will last no more than two consecutive days unless otherwise mutually agreed upon by the Parties. Any resolution of a Dispute by mediation pursuant to this Section 1.1 of these mediation procedures will be in writing and signed by duly authorized representatives of both Parties.

1.2. If the Parties cannot resolve a Dispute in accordance with Section 1.1 of this SCHEDULE 12.1.2, then such Dispute will be resolved by the Parties in accordance with Section 12.2 of the Agreement (Governing Law; Jurisdiction; Venue; Service of Process).

SCHEDULE 12.5

Applicable License Fee Payments in Change of Control

[***]

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788) of Isis Pharmaceuticals, Inc. and in the related Prospectus of our reports dated February 28, 2013, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2012.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2013

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 28, 2013

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

1. I have reviewed this Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 28, 2013

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen

Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc. (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2012, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: February 28, 2013

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	*Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request**.**

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.