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, 2014

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 ☐ No ☐

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 ☐ No ☐

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 ☐ No ☐

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 ☐ No ☐

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. ☐

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

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

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 $3,377,077,105 as of June 30, 2014.*

The number of shares of voting common stock outstanding as of February 23, 2015 was 119,018,331.

DOCUMENTS INCORPORATED BY REFERENCE

The Exhibit Index (Item No. 15) located on pages 146 to 153 incorporates several documents by reference as indicated therein.

* Excludes 19,641,255 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, 2014. 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 drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, and other products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, 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, Inc. and its subsidiaries.

TRADEMARKS

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

Akcea Therapeutics™ is a trademark of Isis Pharmaceuticals, Inc.

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO® is a registered trademark of Genzyme Corporation

KYNAMRO Cornerstone^{SM} is a service mark of Genzyme Corporation

Zytiga® is a registered trademark of Janssen Biotech, Inc.

ABRAXANE® is a registered trademark of Celgene Corporation

Vyndaqel® is a registered trademark of Pfizer Inc.

Glybera® is a registered trademark of uniQure NV

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*.

ISIS PHARMACEUTICALS, INC.

FORM 10-K

For the Fiscal Year Ended December 31, 2014

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PART I

Item 1. Business

Overview

We are the leading company in RNA-targeted drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class 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 with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs. Our business strategy is supported by our platform technology, our robust pipeline of drugs and our multifaceted partnering strategy, which have enabled us to focus on doing what we do best – to discover and develop novel antisense drugs.

We have created a mature and broad pipeline of 38 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We have a number of drugs in later-stage development that we believe represent significant near-term commercial opportunities. ISIS-APOCIII$_{Rx}$ is a drug we designed to treat patients with severely high triglyceride levels, including patients with a severe and rare genetic condition called familial chylomicronemia syndrome, or FCS and patients with partial lipodystrophy, another severe and rare genetic condition. We have completed a broad Phase 2 program in which patients treated with ISIS-APOCIII$_{Rx}$ experienced significantly reduced triglyceride and apolipoprotein C-III, or apoC-III, levels when evaluated as a single agent and in combination with fibrates. We initiated a Phase 3 study in patients with FCS in the third quarter of 2014, with data expected in 2016/2017, that is designed to support a regulatory filing for marketing approval for ISIS-APOCIII$_{Rx}$. In addition to ISIS-APOCIII$_{Rx}$, we are also evaluating ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$ in Phase 3 studies. We designed these drugs to treat patients with severe and rare diseases, such as transthyretin amyloidosis, or TTR, and spinal muscular atrophy, or SMA, who have very limited therapeutic options. The significant unmet medical need and the severity of these diseases could warrant a rapid path to market. We believe all three of these drugs have the potential to reach the market in the next several years. We also have numerous drugs in our pipeline advancing in mid-stage clinical development that could represent significant near and mid-term licensing opportunities. Through February 2015, we and our partners reported clinical data from 20 studies, of which 17 were positive.

Our novel lipid-lowering 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. Genzyme, a Sanofi Company, has also obtained marketing approval in other countries, including Mexico, Argentina, South Korea and Peru, and is pursuing marketing approval in multiple additional markets. Genzyme is evaluating KYNAMRO in a late-stage clinical study, FOCUS FH, in patients with severe heterozygous familial hypercholesterolemia, or HeFH, and they plan to report data from this study in 2015.

The efficiency and broad utility of our drug discovery technology supports the continued growth of our pipeline of antisense drugs. To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. Most recently, we established a wholly owned subsidiary, Akcea Therapeutics, Inc., to develop and commercialize the drugs from our lipid franchise. Akcea will focus on the development and commercialization of ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$, as well as more potent follow on drugs for these programs. To lead Akcea, we hired a senior business leader with commercialization expertise in severe and rare and cardiovascular diseases to maximize the value of our lipid franchise assets. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

Another component of our partnering strategy is to form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as when we licensed KYNAMRO to Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK, Janssen Biotech, Inc. and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Additionally, with Janssen we have a global collaboration to discover and develop antisense drugs to treat autoimmune disorders of the gastrointestinal tract, or GI tract, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs to treat autoimmune disorders in the GI tract. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of companies that can exploit our drugs and technology. We call these companies satellite companies. 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. For example, Regulus Therapeutics, Inc. is a satellite company partner that we co-founded to discover and develop antisense drugs targeting microRNAs. Regulus reported positive clinical data on its anti-miR drug to treat patients with hepatitis C virus. Regulus' stock price increased significantly, which also increased the value of our ownership in Regulus. In response, we sold a small portion of our Regulus stock for more than $20 million of cash. We also maintain our broad ribonucleic acid, or RNA, technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnering strategy, which we designed to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated seven new partnerships that involve antisense drugs for the treatment of various disorders, including neurological diseases, autoimmune disorders of the GI tract and cancer. We formed a broad alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders in the GI tract, four strategic alliances with Biogen Idec to discover and develop antisense drugs to treat neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. Additionally, we and our partner, GSK, are developing five drugs, including ISIS-TTR$_{Rx}$, which is in Phase 3 development. We have the potential to earn significant revenue from these partnerships and our other partnered programs. Since 2007 we have received more than $1.4 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn over $9 billion in future milestone payments and licensing fees from all of our partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements.

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. Through December 2014, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Drug Development Highlights in 2014 and early 2015

- We and Genzyme reported data from a Phase 3 long-term extension study in patients treated with KYNAMRO (mipomersen sodium) injection. In the study, a retrospective analysis of 104 patients with familial hypercholesterolemia treated with KYNAMRO for a mean of one or two years had a significant reduction in major adverse cardiovascular events, or MACE, compared to two years prior to therapy.
  - At the European Society of Cardiology Congress, our KYNAMRO advisor, John Kastelein, M.D., Ph.D., presented an analysis of patients treated with KYNAMRO for one year. These patients experienced a reduction in MACE of 4.85/1000 compared to 25.72/1000 months (in the two years prior to KYNAMRO treatment).
  - At the American Heart Association Meeting, a KYNAMRO principal investigator, P. Bart Duell, M.D., presented an analysis of patients treated with KYNAMRO for two years. These patients experienced a seven-fold reduction in MACE of 3.6/1000 compared to 25.72/1000 months (in the two years prior to KYNAMRO treatment).
- We reported Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high to extremely high triglyceride levels, in patients with type 2 diabetes and high triglycerides and as a single agent as well as in combination with fibrates.
  - At the American College of Cardiology meeting, we presented Phase 2 data on ISIS-APOCIII$_{Rx}$ in combination with fibrates in patients with high triglycerides. In this study, patients achieved statistically significant reductions in triglycerides, apoC-III protein and statistically significant increases in HDL-cholesterol, on top of improvements achieved with each patient's existing therapeutic regimen of triglyceride-lowering drugs.
  - At the Arteriosclerosis, Thrombosis and Vascular Biology meeting, we presented Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with type 2 diabetes and high triglycerides. In this study, patients with diabetes experienced statistically significant decreases in triglyceride levels and statistically significant improvements in glucose control with trends toward enhanced insulin sensitivity.
  - At the National Lipid Association meeting, we presented Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with FCS. FCS is a rare genetic disorder characterized by severely elevated levels of triglycerides. Current treatment options are inadequate and, as a result, patients with FCS have an increased risk of recurrent and potentially fatal pancreatitis and other complications. In this study, patients with extremely high triglycerides experienced substantial reductions of triglycerides that correlated with substantial reductions in triglyceride-rich chylomicrons. We published these data in the New England Journal of Medicine.
  - At the 2014 European Society of Cardiology Congress, our collaborator, John Kastelein, M.D., Ph.D. presented an overview of the ISIS-APOCIII$_{Rx}$ Phase 2 program in which treatment with ISIS-APOCIII$_{Rx}$ produced consistent, robust and statistically significant reductions in triglycerides, apoC-III and non-HDL-cholesterol and increases in HDL-cholesterol in all patient populations evaluated.
- At the European Society of Cardiology Congress, Dr. Sotirios Tsimikas, M.D. presented data from the Phase 1 study of ISIS-APO(a)$_{Rx}$ in healthy volunteers. In this study, ISIS-APO(a)$_{Rx}$ treatment produced dose-dependent and significant reductions in Lp(a) levels in these subjects.
- We reported positive clinical results for ISIS-SMN$_{Rx}$ from two open-label Phase 2 studies in infants and children with SMA, which were consistent with data reported earlier in the year at the American Academy of Neurology meeting. SMA is a severe genetic disease that is the leading genetic cause of infant mortality.
  - At the World Muscle Society Congress, we reported the median event-free age of infants with SMA as of September 2, 2014, which compared favorably to that of infants with SMA in the PNCR natural history study. Time- and dose-dependent increases in muscle function scores were observed in both infants and children with SMA in the on-going study. We presented clinical data showing that ISIS-SMN$_{Rx}$ is distributed throughout the spinal cord and neurons with greater amounts of full-length SMN2 mRNA and SMN protein in tissues from ISIS-SMN$_{Rx}$-treated infants compared to the amounts of full-length SMN2 mRNA and SMN protein in the tissues analyzed from untreated SMA infants.
- At the American Diabetes Association Scientific Sessions, we reported Phase 2 data on ISIS-GCGR$_{Rx}$ demonstrating that patients with type 2 diabetes uncontrolled on stable metformin therapy experienced up to a 2.25 percentage point mean reduction in HbA1c levels after 13 weeks of treatment with ISIS-GCGR$_{Rx}$.

- We reported top-line Phase 2 data on ISIS-PTP1B$_{Rx}$ demonstrating that patients with type 2 diabetes who are uncontrolled on metformin with or without sulfonylurea experienced statistically significant mean reductions in body weight and HbA1c (0.7 percentage point) at 36 weeks.
- At the American Society of Hematology annual meeting, we reported Phase 2 clinical results for ISIS-FXI$_{Rx}$ in patients undergoing total knee replacement. The results showed that ISIS-FXI$_{Rx}$-treated patients experienced a seven-fold lower incidence of venous thromboembolism and numerically fewer bleeding events compared to patients treated with enoxaparin.
    - These data demonstrate that ISIS-FXI$_{Rx}$ can dissociate the antithrombotic effect from the bleeding risk in patients. This is the first time an antithrombotic drug has demonstrated this profile. We published the Phase 2 clinical data of ISIS-FXI$_{Rx}$ in the New England Journal of Medicine
- We reported Phase 2 results showing that ISIS-CRP$_{Rx}$ produced statistically significant mean reductions of CRP protein of 65% with reductions as great as 84% in patients with AF. In addition, two patients who had elevated levels of CRP (>5 mg/L) experienced a reduction of CRP that was associated with a decline to zero in overall AF burden while on treatment.
- ATL reported Phase 2 data on ATL1103 in patients with acromegaly. In this study, ATL reported that treatment with ATL1103 produced a statistically significant average reduction in IGF-1, levels at the 400 mg per week dose.
- OncoGenex reported top-line Phase 2 data on apatorsen (OGX-427) in patients with metastatic bladder cancer. In this study, the Borealis-1 study, OncoGenex reported that treatment with apatorsen in combination with gemcitabine/cisplatin at the 600 mg dose showed a 14 percent reduction in risk of death and a 17 percent reduction in progressive disease and death.
- AstraZeneca presented data from a Phase 1/2 clinical study of ISIS-STAT3-2.5$_{Rx}$ (AZD9150) at the 26th European Organization for Research and Treatment of Cancer. In this study, preliminary evidence of antitumor activity was observed in patients with cancer, including advanced/metastatic hepatocellular carcinoma. Additional data presented at the conference demonstrated that ISIS-STAT3-2.5$_{Rx}$ reduced STAT3 levels in multiple cell types relevant to cancer growth and survival, clinically and pre-clinically. AstraZeneca also presented preclinical data on ISIS-AR-2.5$_{Rx}$ (AZD5312) showing that the drug is active in several tumor models.
- We reported Phase 1 results showing that ISIS-PKK$_{Rx}$ produced significant, dose-dependent reductions of PKK of up to 95 percent in healthy volunteers.
- Regulus reported results from a completed clinical study on RG-101, an anti-miR drug in development to treat patients with hepatitis C virus, or HCV. In this study, a single dose of either 2 mg/kg or 4 mg/kg of RG-101 demonstrated a substantial mean reduction in viral load in patients with varied HCV genotypes and treatment history.
- Together with our partners, we continued to advance our pipeline of drugs.
    - We initiated ENDEAR and CHERISH, Phase 3 studies evaluating ISIS-SMN$_{Rx}$ in infants and children with SMA, respectively.
    - We initiated APPROACH, the Phase 3 study evaluating ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia syndrome.
    - Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections.
    - We initiated a Phase 2 study of ISIS-APO(a)$_{Rx}$ in patients with high levels of lipoprotein(a), an independent risk factor for cardiovascular disease.
    - We initiated a Phase 2 study for ISIS-GCCR$_{Rx}$ in patients with type 2 diabetes.
    - AstraZeneca initiated a Phase 2 study for ISIS-STAT3-2.5$_{Rx}$ in patients with hepatocellular carcinoma.
    - OncoGenex initiated a Phase 2 study for apatorsen in patients with non-small cell lung cancer.
    - We initiated a Phase 1/2 study of ISIS-DMPK-2.5$_{Rx}$ in healthy volunteers and in patients with myotonic dystrophy type 1.
    - Regulus initiated a Phase 1/2 study for RG-101 in healthy volunteers and in patients with HCV.
    - We initiated a Phase 1 study of ISIS-ANGPTL3$_{Rx}$ and ISIS-PKK$_{Rx}$ in healthy volunteers.

- We added twelve drugs to our pipeline.
- We received European Orphan Drug Designation for ISIS-APOCIII$_{Rx}$ for the treatment of patients with familial chylomicronemia syndrome and for ISIS-TTR$_{Rx}$ for the treatment of patients with TTR amyloidosis. We received FDA Orphan Drug Designation for ISIS-DMPK-2.5$_{Rx}$ for the treatment of patients with DM1.

Corporate Highlights in 2014 and early 2015

- We formed a wholly owned subsidiary, Akcea, to develop and commercialize our lipid drugs, ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$, ISIS-ANGPTL3$_{Rx}$ and any follow on drugs for these programs.
  - We appointed Paula Soteropoulos as president and chief executive officer of Akcea. Ms. Soteropoulos will utilize her expertise in commercializing drugs for severe, rare and cardiovascular diseases in global markets to advance Akcea's novel lipid franchise through development and commercialization.
- We formed an alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders of the GI tract. We received $35 million in upfront payments and are eligible to receive nearly $800 million in development, regulatory and sales milestone payments and license fees for the programs under this alliance. We will also receive tiered royalties up to the low double-digits on sales of drugs successfully commercialized.
- We formed an alliance with AstraZeneca to discover and develop novel delivery methods for antisense oligonucleotides. The agreement builds on an existing collaboration between us and AstraZeneca, and supports AstraZeneca's research and development capabilities in the area of antisense oligonucleotide-based therapeutics and RNA biology.
- We strengthened our management team with the addition of Sarah Boyce as chief business officer. Ms. Boyce will provide strategic marketing and business expertise from a commercial background to our management team.
- Abbott obtained CE Mark and launched the Ibis Biosciences diagnostic platform, now called IRIDICA, in Europe. IRIDICA is available in Europe and other CE-Mark recognized countries. IRIDICA was developed from technology discovered by us and transferred to Ibis Biosciences.
- We and Alnylam formed a new agreement that included a cross-license of intellectual property on four disease targets, providing each company with exclusive RNA therapeutic license rights for two programs.
- We successfully completed an offering of $500 million aggregate principal amount of 1 percent convertible senior notes due in 2021 in a private placement. We used a significant amount of the net proceeds from the offering to repurchase a large portion of our 2¾ percent convertible senior notes due 2019.
- We generated more than $250 million in payments from our partners, including the following:
  - $118 million from Biogen Idec, including payments related to advancing ISIS-SMN$_{Rx}$, initiating a Phase 1 study of ISIS-DMPK-2.5$_{Rx}$, validating two undisclosed targets to treat neurological disorders, and selecting two development candidates, ISIS-BIIB3$_{Rx}$ and ISIS-BIIB4$_{Rx}$, to move into our pipeline.
  - $36 million from GSK related to the development of ISIS-TTR$_{Rx}$, ISIS-HBV$_{Rx}$, ISIS-GSK4-L$_{Rx}$ and ISIS-RHO-2.5$_{Rx}$, formerly ISIS-GSK5-2.5$_{Rx}$.
  - $35 million from Janssen related to our alliance to treat autoimmune disorders of the GI tract.
  - $23 million from AstraZeneca related to the development of ISIS-AR-2.5$_{Rx}$ and ISIS-STAT3-2.5$_{Rx}$.
  - $10 million from Alnylam related to Alnylam's license of our technology to its partners.
  - $4 million from Achaogen for the initiation of a Phase 3 study of Plazomicin.
- We received cash through the sale of stock we owned in our satellite company partners of more than $25 million, including more than $20 million from the sale of a portion of our Regulus stock.
- We and our partners were recognized by the drug development community for our innovative and collaborative alliances and our commitment to developing drugs to treat patients with serious, unmet medical needs.
  - We and Genzyme received the 2014 Partners in Progress Corporate Award from the National Organization for Rare Disorders, or NORD, for the development and approval of KYNAMRO, a drug selected for being a very important orphan therapy to reach the market in the United States. This award honors companies that have brought important and innovative treatments to market for patients with rare disorders.
  - Our innovative collaboration with Biogen Idec was voted breakthrough alliance of 2014 by Thomson Reuters Recap.

- We added Joseph Loscalzo, M.D., Ph.D. to our Board of Directors.
- Our senior vice president of research, Frank Bennett, Ph.D., was awarded the Commitment to a Cure Award by the ALS Association for his research and commitment to develop a treatment for ALS.
- Our founder, CEO and chairman of the board of directors, Stanley T. Crooke, M.D., Ph.D., was recognized with several awards.
  - The prestigious SCRIP Lifetime Achievement Award.
  - The SMA Breakthrough Award by CURE SMA.

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 typically antisense drugs interrupt the production of disease-causing proteins by targeting 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 or degrade the RNA.

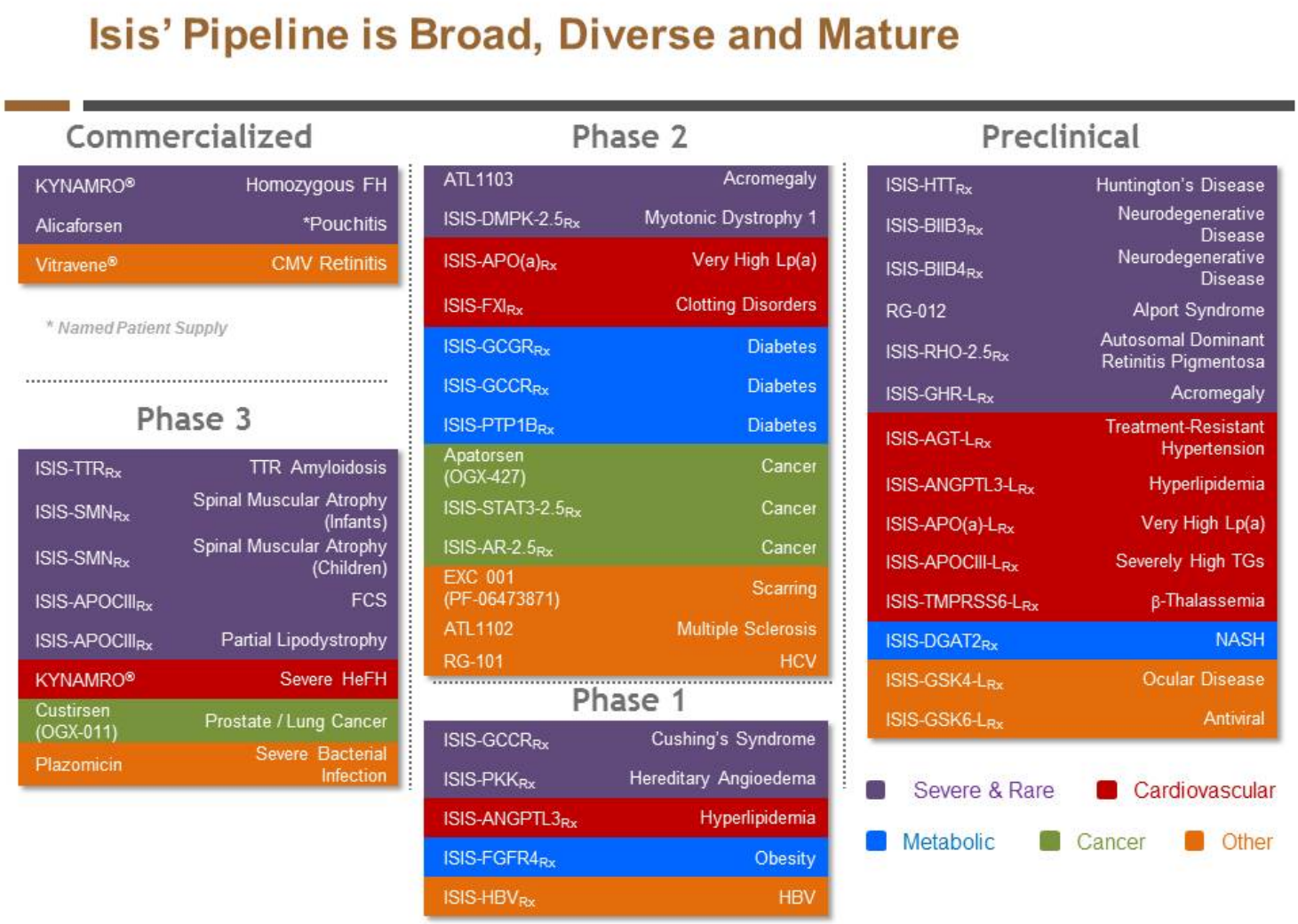
Our Development Projects

We are the leader in the discovery and development of an exciting class of RNA-targeted drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs from 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, with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, 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, building a broad proprietary portfolio of drugs applicable to many disease targets and creating opportunities to generate substantial revenue. 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 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 further increases the potency of our drugs and could make oral administration commercially feasible. We currently have four generation 2.5 drugs in development, ISIS-AR-2.5$_{Rx}$, ISIS-DMPK-2.5$_{Rx}$, ISIS-RHO-2.5$_{Rx}$ and ISIS-STAT3-2.5$_{Rx}$, and we expect that some of our future drugs will also incorporate our generation 2.5 chemistry. In addition to improving the chemical foundation of our drugs, we have also created ligand-conjugated antisense, or LICA, technology, which we designed to enhance the delivery of our drugs to particular tissues. We believe that our LICA technology could further enhance the potency of our drugs. For example, our LICA technology directed toward liver targets produced a ten-fold increase in potency in preclinical studies in both our second-generation and our generation 2.5 drugs. We currently have eight second generation-LICA drugs in our pipeline, ISIS-AGT-L$_{Rx}$, ISIS-ANGPTL3-L$_{Rx}$, ISIS-APO(a)-L$_{Rx}$, ISIS-APOCIII-L$_{Rx}$, ISIS-GHR-L$_{Rx}$, ISIS-GSK4-L$_{Rx}$, ISIS-GSK6-L$_{Rx}$, and ISIS-TMPRSS6-L$_{Rx}$, all of which we designed to inhibit targets in the liver. We expect we can also enhance some of our future drugs, including our generation 2.5 drugs, with our LICA technology.

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 commercialized products and each of our and our partners' drug development projects, their targets, disease indications and the development status of each. Typically, we identify our drugs by the target, such as ISIS-APOCIII$_{Rx}$ or ISIS-SMN$_{Rx}$. Unless indicated otherwise, the majority of the drugs in our pipeline are second generation antisense drugs. For our generation 2.5 drugs, we differentiate these drugs by adding a 2.5 notation at the end of the drug name. For our LICA drugs, we differentiate by adding an L at the end of the drug name. We also plan to add generation 2.5 drugs that incorporate our LICA technology. We will identify these drugs by the addition of both the 2.5 and L into the drug name. For some of our partnered drugs, we refer to a drug by the partner's own compound number, such as ATL1103 or RG-101. 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.



KYNAMRO (mipomersen sodium) injection

Our flagship product, KYNAMRO, is being marketed in the United States by Genzyme for patients with HoFH. These are patients who are at high cardiovascular risk and who are not able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies. KYNAMRO was approved by the FDA in January 2013 as an adjunct to lipid-lowering therapy and diet to reduce LDL-C, apolipoprotein-B, or apo-B, total cholesterol and non-high-density lipoprotein-cholesterol, or non-HDL-cholesterol, 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 executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options for HoFH. Genzyme has obtained marketing approval for KYNAMRO in the United States, South Korea, Argentina, Mexico and Peru for use in patients with HoFH and is continuing to pursue approval in multiple additional markets. In order to reach patients with HoFH in the United States, Genzyme is concentrating marketing and sales efforts on lipid specialists, cardiologists, and physicians who treat these types of patients. In the United States, Genzyme has established the KYNAMRO Cornerstone, a program offering services related to HoFH and KYNAMRO, including dedicated case management, reimbursement support, financial assistance for those who qualify, in-person injection training, and disease and product education for healthcare providers, patients, families, and caregivers. Genzyme also continues to raise awareness of HoFH. These activities include supporting continued medical educational programs to inform physicians about HoFH and partnering with key advocacy groups, such as the Familial Hypercholesterolemia Foundation, the National Lipid Association, American College of Cardiology, the International Symposium on Atherosclerosis and the American Heart Association.

KYNAMRO is a novel, first-in-class, apo-B synthesis inhibitor for the reduction of LDL-C. It is an 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 a randomized, double-blind, placebo-controlled trial in HoFH patients. In this multi-center trial, KYNAMRO significantly further reduced LDL-C and all other measured endpoints when added to a treated baseline. In this trial, four patients (11 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 heterozygous 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 the diagnosis of HoFH. There are multiple diagnostic criteria, which may include:

- DNA evidence confirming the presence of specific gene mutations associated with a genetic diagnosis of HoFH. However, DNA evidence is generally not necessary for diagnosis and genetic analysis may be inconclusive;
- Family history, if known, of premature coronary heart disease and hypercholesterolemia;
- Presence of premature heart disease;
- Elevated plasma levels of total cholesterol and LDL-C;
- Physical examination for signs of cholesterol deposits, including xanthomas on the backs of hands, fingers, face and other areas of the skin. Xanthomas may not be present in every patient; and
- Suboptimal response to lipid lowering therapy.

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 removes LDL-C from the blood and until recently it has been the primary therapy available on top of maximally tolerated lipid-lowering therapy.

Clinical Development

In conjunction 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 ages 12 to 53 years, including seven patients ages 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 Raal 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 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-cholesterol, and lipoprotein a, or Lp(a). These key lipids are generally accepted risk factors for cardiovascular disease. Data from these studies were published in Circulation, PLoS One and the Journal of the American College of Cardiology.

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 two 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.

In January 2013, the FDA approved the New Drug Application, or NDA, for KYNAMRO for use in patients with HoFH.

In 2012, Genzyme initiated a Phase 3 study titled "evaluating the saFety and atherOgeniC lipoprotein redUction of mipomerSen in FH", or FOCUS FH. 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. Genzyme has completed enrollment in this study and plans to have data in the middle of 2015.

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 and neurological disorders 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. ISIS-SMN_{Rx}, the most advanced neurological drug in our pipeline, is now in two Phase 3 studies for the treatment of infants and children with SMA.

We are discovering and developing antisense drugs to treat severe and rare and neurological diseases for which there is a need for new treatment options. We have established strategic alliances in drug development areas that are high risk or in which our partners have significant expertise and resources to allow us to expand our drug discovery and development efforts beyond what we would choose to do internally. For example, our strategic partnerships with Biogen Idec and Roche have supported advancing five drugs for the treatment of neuromuscular or neurological diseases in our pipeline.

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.

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 our pipeline table.

Alicaforsen — Atlantic Pharmaceuticals Limited is developing and selling alicaforsen through a named patient program. A named patient program allows Atlantic to sell alicaforsen in response to physicians' requests under international named patient supply regulations for patients with pouchitis and other indications. Alicaforsen is an antisense drug designed to target the 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 European Medicines Agency, or EMA, have since granted alicaforsen Orphan Drug Designation for the treatment of pouchitis in the United States and Europe, respectively. We are eligible to receive royalties on product sales, including product sales under the named patient supply program from Atlantic Pharmaceuticals. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

ISIS-TTR$_{Rx}$ — ISIS-TTR$_{Rx}$ is an antisense drug we designed to treat 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, such as the heart, peripheral nerves, and the GI 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.

We are evaluating ISIS-TTR$_{Rx}$ to treat two 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.

ISIS-TTR$_{Rx}$ is the first drug to enter development under our preferred partner alliance with GSK. 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. 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 an average of 75 percent reduction in TTR protein, with some subjects achieving approximately 90 percent reduction. In addition, there were several subjects that reached TTR protein levels that were below the limit of assay detection. Subjects treated with ISIS-TTR$_{Rx}$ generally tolerated the drug well.

In February 2013, we initiated a randomized, double-blind, placebo-controlled 15-month Phase 3 study of ISIS-TTR$_{Rx}$ in patients with FAP. In this study, we are evaluating the efficacy of ISIS-TTR$_{Rx}$ by measuring neurological dysfunction and quality of life in patients with FAP. We already have patients who have completed all fifteen months of treatment and are currently receiving ISIS-TTR$_{Rx}$ in an open-label extension study. We plan to report data in 2017. Our partner, GSK, also plans to evaluate ISIS-TTR$_{Rx}$ in patients with FAC and is in the planning stages of a Phase 3 study for this indication.

***ISIS-SMN*$_{Rx}$** — ISIS-SMN$_{Rx}$ is an antisense drug we discovered in collaboration with Dr. Adrian R. Krainer at Cold Spring Harbor Laboratory. We designed ISIS-SMN$_{Rx}$ to treat 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, carry the gene mutation that causes SMA. 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 neuromuscular growth and function. The severity of SMA correlates with the amount of SMN protein. Infants with Type I SMA, the most severe life-threatening form, produce very little SMN protein and have a significantly 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.

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$_{Rx}$. 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. We developed a biomarker assay to measure levels of SMN protein in the cerebral spinal fluid of children and infants with SMA. In February 2014, we reported the first set of data using this biomarker assay. Using this assay, we observed dose-dependent increases in SMN protein levels in children with SMA treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies. In the single-dose study, SMN protein levels more than doubled in the two highest dose cohorts, 6 mg and 9 mg, with average increases of approximately 120 percent and 160 percent compared to baseline, respectively, approximately nine to 14 months after dosing. Similarly, in the multiple-dose study, we observed substantial increases in SMN protein levels in the 9 mg cohort of 115 percent compared to baseline approximately three months after the first dose. In October 2014, we reported results from an analysis of spinal cord tissue samples from autopsies showing that ISIS-SMN$_{Rx}$ is distributed throughout the central nervous system. The results of these analyses also showed greater levels of full length SMN2 mRNA and full length SMN protein in tissues in ISIS-SMN$_{Rx}$-treated SMA infants compared to the levels of SMN2 mRNA and full length SMN protein in the tissues analyzed from untreated SMA infants.

We are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA. We reported an update on this study in October 2014 at the World Muscle Society Congress with a data cut off of September 2, 2014. In this study, we measured changes in muscle function scores using the Hammersmith Functional Motor Scale-Expanded, or HFMSE, in children treated with multiple doses of ISIS-SMN$_{Rx}$. We reported that children in the 3 mg, 6 mg and 9 mg cohorts achieved mean increases in muscle function scores from baseline of 1.7, 3.2 and 2.3, respectively, eight to 13 months after last dose. These data are consistent with previously reported HFMSE scores for these children nine months after their last dose, which were reported in April 2014. We also reported that increases in muscle function scores were observed eight to 13 months after last dose in the six-minute walk test, or 6MWT, and the upper limb mobility, or ULM, test. In the 6MWT, performed with 10 ambulatory children, a mean increase of 24.4 meters was observed 12 to 16 months after the patients' baseline visits, compared to the previously reported increase of 22.7 meters at nine months. In the ULM test, a mean increase of 3.1 points was observed 11 to 16 months after the patients' baseline visits, compared to the previously reported increase of 2.3 points at nine months.

We are also evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in 20 infants who have been diagnosed with SMA. We reported an update on this study in October 2014 with a data cut off of September 2, 2014. We reported a median event-free age of 16.3 months in the infants in the 6 mg cohort. For the infants in the 12 mg cohort, which began dosing five months after the initiation of dosing for the 6 mg cohort, we reported a median event-free age of 11.6 months. These data compared favorably to the natural history of infants with SMA as published by the Pediatric Neuromuscular Clinical Research Network, or PNCR, in the journal *Neurology*. As reported in October 2014, there had been four events (one permanent ventilation and three deaths, all related to respiratory infections) in the 16 infants in the 12 mg cohort and two events (one permanent ventilation and an accidental death) in the four infants in the 6 mg cohort. We also observed increases in muscle function scores in infants from both dose cohorts.

The safety and tolerability profile of ISIS-SMN$_{Rx}$ to date supports continued development. The lumbar puncture procedure in SMA infants and children has been well tolerated and shown to be feasible. Furthermore, as of September 2014, we had administered a total of 250 intrathecal doses of ISIS-SMN$_{Rx}$, and the procedure was well tolerated. In all infants and children dosed, there have been no drug-related serious adverse events, or SAEs. Most of the adverse events, or non-SAEs, have been mild or moderate in severity and not related to drug. There were no changes in the safety profile with repeated doses of ISIS-SMN$_{Rx}$.

We are evaluating ISIS-SMN$_{Rx}$ in two Phase 3 studies in infants and children with SMA. We designed these studies to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe. The Phase 3 study, ENDEAR, is a randomized, double-blind, sham-procedure controlled 13-month study in approximately 110 infants with SMA. In this study, we are evaluating the efficacy of ISIS-SMN$_{Rx}$ by measuring the time to permanent ventilation or survival. The Phase 3 study, CHERISH, is a randomized, double-blind, sham-procedure controlled 15-month study in approximately 117 children with SMA. In this study, we are evaluating the efficacy of ISIS-SMN$_{Rx}$ by measuring changes in muscle function scores. We initiated both of these studies in 2014 and plan to report data from both of these studies in the 2016/2017 timeframe.

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 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 apoC-III protein production and lower triglycerides. ApoC-III regulates triglyceride metabolism in the blood and is an independent cardiovascular risk factor. The fact that people who have certain mutations in the gene for apoC-III that result in lower levels of apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease supports our approach. Also, people with elevated levels of apoC-III have increased dyslipidemia associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In addition, people with elevated triglycerides are at increased risk for type 2 diabetes, and people with severely elevated triglycerides are at high risk for acute pancreatitis and other serious conditions. Results from our studies support our continued advancement of ISIS-APOCIII$_{Rx}$.

ISIS-APOCIII$_{Rx}$ is the most advanced drug in our lipid franchise. We plan to transition the development of ISIS-APOCIII$_{Rx}$ to Akcea, our wholly owned subsidiary, which is also responsible for conducting commercial activities. ISIS-APOCIII$_{Rx}$ is in development to treat patients with partial lipodystrophy and patients with FCS. Both partial lipodystrophy and FCS are rare orphan diseases, and each one affects approximately one to two out of a million people. Patients with partial lipodystrophy have diabetes and other metabolic abnormalities, including elevated triglycerides, which increases their risk of pancreatitis. We believe that the robust triglyceride reduction and the improvements in glucose control we observed in our Phase 2 program support our evaluation of ISIS-APOCIII$_{Rx}$ in this patient population. FCS patients often have triglyceride levels higher than 2,000 mg/dL and experience a number of health problems such as recurrent acute pancreatitis that often requires hospitalization, abdominal pain, and enlargement of the liver and spleen. We believe that the significant unmet medical need for an effective triglyceride-lowering drug for patients with FCS and partial lipodystrophy and the robust, consistent effects we observed with ISIS-APOCIII$_{Rx}$ should enable us to rapidly move this program forward toward the market.

In preclinical studies, ISIS-APOCIII$_{Rx}$ diminished signs of metabolic syndrome and reduced atherosclerosis in mice. In a Phase 1 study in healthy volunteers, ISIS-APOCIII$_{Rx}$ produced rapid, dose-dependent median reductions in blood of up to 78 percent in apoC-III protein levels and up to 44 percent in triglyceride levels.

We completed a broad Phase 2 program evaluating ISIS-APOCIII$_{Rx}$ in patients with high, very high, and severely high triglycerides, in patients with type 2 diabetes and in patients with FCS. We also evaluated ISIS-APOCIII$_{Rx}$ both as a single agent and in combination with fibrates. Patients in our Phase 2 program entered with baseline triglyceride levels ranging from moderately high to severely high. In all patient groups treated with ISIS-APOCIII$_{Rx}$, irrespective of their incoming triglyceride levels, we observed consistent reductions in apoC-III, triglycerides and apoC-III-associated very low-density lipoprotein, or VLDL, complexes, and increased HDL, with a positive effect on non-HDL. Data from the 300 mg/week dose from each of these studies are summarized in the table below.

Comparison of Patients Treated with 300 mg/wk of ISIS-APOCIII$_{Rx}$

	Single Agent in Diabetics with High TG	Single Agent in Very High TG	In Addition to Fibrates in Very High TG	Single Agent in FCS
Baseline Mean mg/dL [range]				
ApoC-III	14 [9-20]	23 [14-33]	18 [12-30]	25 [19-35]
Triglycerides	260[167-361]	559 [291-952]	394 [224-932]	1844 [1406-2083]
HDL-C	41[29,55]	34 [22-52]	34 [14-53]	13 [8-16]
Non-HDL-C	172 [128-300]	175 [76-312]	185 [118-243]	262 [214-327]
Mean % Change from Baseline (SD)				
ApoC-III	-88% (5.4)	-80% (9.3)	-71% (13.0)	-81% (9.8)
Triglycerides	-69% (10.1)	-71% (14.1)	-64% (8.9)	-69% (15.6)
HDL-C	+42% (32.2)	+46% (24.0)	+52% (23.7)	+78% (74.6)
Non-HDL-C	-22% (18.5)	-11% (38.3)	-19% (28.8)	-58% (14.3)

The safety and tolerability profile of ISIS-APOCIII$_{Rx}$ supports continued development. The most common adverse event was injection site reactions, which were predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no treatment-related elevations in liver enzymes greater than three times the upper limit of normal, no abnormalities in renal function and no clinically meaningful changes in other laboratory values.

In December 2014, we published results from the Phase 2 study of ISIS-APOCIII$_{Rx}$ in patients with FCS in the New England Journal of Medicine.

We are evaluating ISIS-APOCIII$_{Rx}$ in a Phase 3 study in patients with FCS. The Phase 3 study, APPROACH, is a randomized, double-blind, placebo-controlled 52-week study in approximately 50 patients with FCS. In this study, we are evaluating the efficacy of ISIS-APOCIII$_{Rx}$ by measuring the percent change in fasting triglycerides from baseline after three months of dosing. We plan to initiate a Phase 3 study in patients with partial lipodystrophy in 2015. We are designing this study to support a regulatory filing for ISIS-APOCIII$_{Rx}$ in patients with partial lipodystrophy. In early 2015, we initiated a second Phase 3 study, COMPASS, in patients with triglycerides greater than 500 mg/dL. We are designing this study to provide additional clinical experience and safety data to support our regulatory filings for FCS and partial lipodystrophy. We plan to report data from these studies in the 2016/2017 timeframe.

ATL1103 — ATL1103 is an antisense drug designed to target 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 and has completed a Phase 1 study in healthy volunteers demonstrating that ATL1103 was safe and well tolerated. ATL has also completed a Phase 2 study of ATL1103 in patients with acromegaly. In September 2014, ATL reported results from this study showing a statistically significant average reduction in serum IGF-I levels of 26 percent from baseline at week 14 with the 400 mg per week dose, the highest dose tested. ATL reported that ATL1103 was generally well tolerated in the study. The most common adverse event was injection site reactions, which were predominantly mild and typically resolved within days. ATL plans to initiate a small study at a higher dose than 400 mg per week.

ISIS-DMPK-2.5$_{Rx}$ — ISIS-DMPK-2.5$_{Rx}$, formerly ISIS-DMPK$_{Rx}$, is a generation 2.5 antisense drug we designed to correct the underlying genetic defect that causes Myotonic Dystrophy Type 1, or DM1. DM1 is a rare genetic neuromuscular disease primarily characterized by progressive muscle atrophy, weakness and myotonia. DM1 is the most common form of muscular dystrophy in adults and affects approximately 150,000 patients in the United States, Europe and Japan. Patients with DM1 have a genetic defect in their DMPK, or dystrophia myotonica-protein kinase, gene in which a sequence of three nucleotides repeats extensively, creating an abnormally long RNA, which becomes toxic as it accumulates in the nucleus of cells and prevents the production of proteins needed for normal cellular function. The number of triplet repeats increases from one generation to the next, resulting in the possibility of more severe disease in each subsequent generation. There are currently no disease-modifying therapies that address the disease. The FDA granted Orphan Drug Designation to ISIS-DMPK-2.5$_{Rx}$ for the treatment of patients with DM1.

In 2012, we and Biogen Idec entered into an alliance that provides Biogen Idec an option to develop and commercialize ISIS-DMPK-2.5$_{Rx}$. We designed ISIS-DMPK-2.5$_{Rx}$ to target DMPK and reduce the toxic DMPK RNA in the cells. In preclinical studies, we showed that an antisense compound targeting the DMPK messenger RNA, or mRNA, entered muscle cells and significantly reduced the toxic RNA. Effective reduction of toxic RNA led to a reversal of the disease symptoms that was sustained for up to one year after treatment in a mouse model of DM1. By removing toxic RNA, ISIS-DMPK-2.5$_{Rx}$ could be an effective approach to treating patients with DM1.

We are evaluating ISIS-DMPK-2.5$_{Rx}$ in a randomized, placebo-controlled, dose-escalation Phase 1/2 clinical study in patients with DM1 and plan to report data from this study in late 2015 or early 2016.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug we designed to target 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. For more information on ISIS-GCCR$_{Rx}$ and type 2 diabetes, please refer to the ISIS-GCCR$_{Rx}$ section under the subheading "Metabolic Disease Franchise".

ISIS-PKK$_{Rx}$ — ISIS-PKK$_{Rx}$ is an antisense drug we designed to inhibit the production of prekallikrein, or PKK, a protein produced in the liver that plays an important role in the activation of inflammatory mediators associated with acute attacks of hereditary angioedema, or 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 have completed a Phase 1 study evaluating ISIS-PKK$_{Rx}$ in healthy volunteers in which we observed up to 95% reduction of PKK. In this study, ISIS-PKK$_{Rx}$ was generally well tolerated.

We plan to initiate a Phase 2 clinical study evaluating ISIS-PKK$_{Rx}$ in patients with hereditary angioedema in 2015.

Preclinical Development

The table below lists our preclinical drugs in our severe and rare disease franchise.

Drug	Indication	Partner
ISIS-HTT$_{Rx}$	Huntington's Disease	Roche
ISIS-BIIB3$_{Rx}$	Neurodegenerative Disease	Biogen Idec
ISIS-BIIB4$_{Rx}$	Neurodegenerative Disease	Biogen Idec
RG-012	Alport Syndrome	Regulus
ISIS-RHO-2.5$_{Rx}$	Autosomal Dominant Retinitis Pigmentosa	GSK
ISIS-GHR-L$_{Rx}$	Acromegaly	Isis owned

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. We have designed the majority of the drugs in our cardiovascular franchise to target cardiovascular risk factors. These drugs make up our lipid franchise and include ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$. ISIS-APOCIII$_{Rx}$ is the most advanced drug in this franchise and is designed to lower apoC-III and triglycerides, which are both independent risk factors for cardiovascular disease. In addition, two independent publications showed that people with rare mutations in the APOCIII gene have lower triglyceride levels and reduced risk of developing coronary heart disease. Results of these studies support the continued advancement of ISIS-APOCIII$_{Rx}$. Recent additions to our lipid franchise are our drugs that lower Lp(a) and angiopoietin-like 3 protein, or ANGPTL3. Lp(a) is another independent risk factor for cardiovascular disease. ANGPTL3 is a genetically validated target shown to play a significant role in regulating lipid levels. Humans who do not produce a functional ANGPTL3 protein due to a genetic mutation have extremely low levels of cholesterol, LDL-C, and very low levels of triglycerides and HDL-cholesterol. Currently available lipid-lowering therapies do not significantly lower apoC-III, triglycerides, Lp(a), or ANGPTL3. We believe that reducing levels of apoC-III, Lp(a) and ANGPTL3 could provide a complimentary approach to lipid-lowering therapies, including KYNAMRO. We are also developing follow-on LICA antisense drugs for the three drugs in our lipid franchise.

In order to maximize the value of our lipid franchise, while also maintaining control over the development and commercialization of these assets, we have created a wholly owned subsidiary, Akcea Therapeutics. Akcea is focused on the development and commercialization of our lipid franchise drugs and their follow on compounds.

In addition to our lipid franchise drugs, we have a promising anticoagulant agent, ISIS-FXI$_{Rx}$, in development in our cardiovascular disease franchise. We recently reported Phase 2 data on ISIS-FXI$_{Rx}$ showing that ISIS-FXI$_{Rx}$-treated patients experienced a seven-fold lower incidence of venous thromboembolism and numerically fewer bleeding events compared to patients treated with enoxaparin, a commonly used anticoagulant. These data demonstrate that for the first time, an anticoagulant, ISIS-FXI$_{Rx}$, can prevent clotting without increasing bleeding, two biological events that were previously inseparable. Our latest drug to enter the franchise, ISIS-AGT-L$_{Rx}$, offers a novel approach to treating patients with high blood pressure.

ISIS-APO(a)$_{Rx}$ — ISIS-APO(a)$_{Rx}$ 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. Lp(a) levels in blood can vary greatly between individuals due primarily to genetic variations between individuals. Lp(a) levels are genetically determined, reached by the age of two and remain constant throughout the life of the individual. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies do not adequately reduce Lp(a) to acceptable levels in patients with elevated Lp(a). As a general guideline for ideal Lp(a) levels, the European Atherosclerosis Society recommends that Lp(a) be less than or equal to 50 mg/dL. Even patients who can control their LDL-C 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).

ISIS-APO(a)$_{Rx}$ is part of our lipid franchise and, as such, we plan to transition development activities associated with ISIS-APO(a)$_{Rx}$ to Akcea, our wholly owned lipid subsidiary. We are developing ISIS-APO(a)$_{Rx}$ to treat patients with high Lp(a) levels who have either coronary heart disease or aortic stenosis. Both of these groups of patients are at high risk of cardiovascular events.

We completed a Phase 1 study evaluating ISIS-APO(a)$_{Rx}$ in healthy volunteers with incoming Lp(a) levels ranging from 10 mg/dL to 98 mg/dL. In this study, we reported dose-dependent reductions of up to 95 percent in Lp(a). In addition to Lp(a) activity, subjects treated with 300 mg of ISIS-APO(a)$_{Rx}$ experienced an up to 59 percent reduction in oxidized phospholipids, lipids that play an important role in proinflammatory and proatherogenic processes believed to be associated with Lp(a). In this study, ISIS-APO(a)$_{Rx}$ was generally well tolerated.

We are currently evaluating ISIS-APO(a)$_{Rx}$ in a Phase 2 study in patients with elevated levels of Lp(a) (greater than 50 mg/dL). We plan to report data from this study in late 2015 or early 2016.

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 that can be responsible for 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. 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.

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 2 comparator-controlled study evaluating the incidence of venous thromboembolic events, or VTE, in patients treated with ISIS-FXI$_{Rx}$ undergoing total knee replacement surgery, or total knee arthroplasty, or TKA. In December 2014, we reported these data at the American Society of Hematology meeting and also published these data in the New England Journal of Medicine. In this study, we showed that ISIS-FXI$_{Rx}$-treated patients experienced a dose-dependent decrease in venous thromboembolic events. Patients treated with 300 mg of ISIS-FXI$_{Rx}$ experienced a seven-fold lower rate of VTE as compared with those treated with enoxaparin (4.2% and 30.4%, respectively; $p<0.001$). Patients treated with 200 mg of ISIS-FXI$_{Rx}$ had a rate of VTE comparable to that in patients treated with enoxaparin (26.9% and 30.4%, respectively). The rate of VTE in patients given enoxaparin is within the range documented in previous studies in this therapeutic setting. ISIS-FXI$_{Rx}$ treatment was associated with a dose-dependent and sustained reduction in Factor XI activity that correlated with the lower rate of VTE. The rate of bleeding was low with ISIS-FXI$_{Rx}$ and enoxaparin. We also reported that in this study, ISIS-FXI$_{Rx}$ was generally well tolerated. There were no observed differences in safety outcomes compared with enoxaparin. In particular, there were no flu-like symptoms, and injection site reactions were infrequent and mild. There have been no drug-related serious adverse events reported to date.

We believe that there are a number of opportunities to develop ISIS-FXI$_{Rx}$ as an antithrombotic for patients who require a safer and more effective agent. We plan to evaluate ISIS-FXI$_{Rx}$ in patient populations with an unmet need in which relatively small studies can be conducted such as patients with atrial fibrillation, or AF, and end-stage renal disease. We also believe that ISIS-FXI$_{Rx}$ can potentially be used in broader indications, including in patients with mechanical heart valves and to prevent secondary cardiovascular events in patients with acute coronary syndrome. In 2015 we plan to initiate a Phase 2 study in patients with renal failure.

ISIS-ANGPTL3$_{Rx}$ — ISIS-ANGPTL3$_{Rx}$ is an antisense drug we designed to reduce ANGPTL3, an independent risk factor for cardiovascular disease. ANGPTL3 is produced in the liver and regulates lipid, glucose and energy metabolism. Humans with elevated levels of ANGPTL3 have hyperlipidemia that is associated with an increased risk of premature heart attacks, increased arterial wall thickness as well as multiple metabolic abnormalities, such as insulin resistance. In contrast, humans with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and a lower risk of cardiovascular disease. In preclinical studies, antisense inhibition of ANGPTL3 resulted in robust reductions of multiple lipid parameters, including total-cholesterol, LDL-C and triglycerides.

ISIS-ANGPTL3$_{Rx}$ is part of our lipid franchise and, as such, we plan to transition development activities associated with ISIS-ANGPTL3$_{Rx}$ to Akcea. We plan to complete a Phase 1 study evaluating ISIS-ANGPTL3$_{Rx}$ in healthy volunteers.

Preclinical Development

The table below lists our preclinical drugs in our cardiovascular disease franchise.

Drug	Indication	Partner
ISIS-AGT-L$_{Rx}$	Treatment-Resistant Hypertension	Isis owned
ISIS-ANGPTL3-L$_{Rx}$	Hyperlipidemia Disease	Akcea
ISIS-APO(a)-L$_{Rx}$	Very High Lp(a)	Akcea
ISIS-APOCIII-L$_{Rx}$	Severely High TGs	Akcea
ISIS-TMPRSS6-L$_{Rx}$	b-Thalassemia	Isis owned

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 29 million people in the United States, or nine 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 and development efforts. Our approach is to develop antisense drugs that doctors can add to existing therapies to treat diabetes. 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.

We have reported positive Phase 2 data from ISIS-GCGR$_{Rx}$ and ISIS-PTP1B$_{Rx}$, the most advanced drugs in our metabolic franchise. These two drugs and our third drug, ISIS-GCCR$_{Rx}$, are designed to act 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.

ISIS-GCGR$_{Rx}$ — ISIS-GCGR$_{Rx}$ is an antisense drug we designed to target 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.

We are developing ISIS-GCGR$_{Rx}$ to help provide better glucose control for patients with type 2 diabetes. In preclinical studies using the most insulin-resistant models of type 2 diabetes, 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, including increases in lipids and blood pressure, limiting their potential use as drugs.

We have completed a Phase 1 study evaluating the safety of ISIS-GCGR$_{Rx}$ in healthy volunteers. In this study ISIS-GCGR$_{Rx}$ was generally well tolerated with no clinically significant increases in lipids or blood pressure and with no hypoglycemic events.

We have completed a Phase 2 placebo-controlled study evaluating ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes. In June 2014, we reported these data at the American Diabetes Association meeting. In this study, we showed that patients treated with ISIS-GCGR$_{Rx}$ in addition to metformin achieved absolute mean reduction in hemoglobin A1c, or HbA1c, of up to 2.25 percentage points from baseline after only 13 weeks of treatment. Patients receiving placebo had a 0.25 percentage point reduction in HbA1c. In this study, more than half of the patients in the per protocol cohort achieved an HbA1c level of less than or equal to 7.0 percent. Patients treated with ISIS-GCGR$_{Rx}$ in this study also achieved a mean reduction of up to 74.9 μmol/L in fructosamine. In addition, in these patients a mean increase in total GLP-1 of up to 19.97 pmol/L was observed.

In this study ISIS-GCGR$_{Rx}$ was generally well tolerated. The most common adverse event was infrequent injection site reactions, which were predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no abnormalities in renal function and no cases of symptomatic hypoglycemia. ISIS-GCGR$_{Rx}$ was not associated with clinically meaningful increases in LDL-C, triglycerides, blood pressure or body weight gain (side effects associated with some small molecule inhibitors of glucagon receptor). As has been observed with small molecule inhibitors of glucagon receptor and consistent with the pharmacology of glucagon receptor inhibition, liver enzyme elevations that were neither associated with elevated bilirubin nor other indicators of liver damage were observed. Liver enzyme elevations were much less frequent and lower in the 100 mg dose cohort compared to the 200 mg dose cohort and declined after dosing discontinued. There were no clinically meaningful changes in other laboratory values.

We plan to conduct additional studies to identify the optimal dose and schedule to achieve glucose control with manageable glucagon receptor-related liver enzyme elevations. Given the unique mechanism of action and good tolerability observed, 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.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug we designed to target the 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. Our antisense inhibitor of GCCR takes advantage of the unique tissue distribution of oligonucleotides that allows our drug 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, ISIS-GCCR$_{Rx}$ was generally well tolerated 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. For more information on ISIS-GCCR$_{Rx}$ and Cushing's Syndrome, please refer to the ISIS-GCCR$_{Rx}$ section under the subheading "Severe and Rare Disease Franchise".

We plan to report data from a Phase 2 study of ISIS-GCCR$_{Rx}$ in patients with type 2 diabetes in combination with metformin in 2015.

ISIS-PTP1B$_{Rx}$ — ISIS-PTP1B$_{Rx}$ is an antisense drug we designed to target 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 patients with 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.

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 reported top-line data from a Phase 2 study of ISIS-PTP1B$_{Rx}$ in patients with type 2 diabetes with or without sulfonylurea therapy. In this study, patients treated with ISIS-PTP1B$_{Rx}$ achieved statistically significant reductions in body weight and HbA1c. In patients treated with ISIS-PTP1B$_{Rx}$, a mean reduction in HbA1c of 0.7 percentage points from baseline was achieved at 36 weeks, compared to a mean reduction of 0.2 percentage points for placebo-treated patients (p=0.03). Patients treated with ISIS-PTP1B$_{Rx}$ also experienced a statistically significant mean reduction in body weight from baseline at 36 weeks (p=0.01). Patients received 200 mg of ISIS-PTP1B$_{Rx}$ or placebo for 26 weeks added to their stable doses of their background therapies. In this study, the average incoming HbA1c level was 8.6 percent and the average BMI was 34 kg/m2. Patients in this study were not required to conform to any type of restrictive or weight-loss diet beyond the standard dietary restrictions they adhered to upon entry into the study. In this study ISIS-PTP1B$_{Rx}$ was generally well tolerated. The most common adverse event was infrequent injection site reactions, which were predominantly mild and resolved rapidly. We plan to report the full data from this study at a scientific meeting in 2015.

We believe that physicians may use ISIS-PTP1B$_{Rx}$ in combination with most of the other commonly used diabetes 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.

ISIS-FGFR4$_{Rx}$ — ISIS-FGFR4$_{Rx}$ is an antisense drug we designed to target fibroblast growth factor receptor 4, or FGFR4, in the liver and fat tissues. Reducing FGFR4 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 central nervous system, or 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 initiate a Phase 2 study in obese patients in 2015.

Preclinical Development

The table below lists our preclinical drug in our metabolic franchise.

Drug	Indication	Partner
ISIS-DGAT2$_{Rx}$	NASH	Isis owned

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 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 expands our anti-cancer efforts and supports an aggressive and broad clinical development plan for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. AstraZeneca brings significant experience that enables 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, data from a Phase 1/2 clinical study of ISIS-STAT3-2.5$_{Rx}$ showed evidence of antitumor activity in patients with cancer, including advanced/metastatic hepatocellular carcinoma.

Custirsen — OncoGenex is developing Custirsen, formerly OGX-011, an antisense drug designed to target clusterin. Clusterin is 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. OncoGenex is 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 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.

OncoGenex is conducting a global Phase 3 clinical program in patients with CRPC and metastatic NSCLC. OncoGenex reported results from the Phase 3 SYNERGY study evaluating custirsen as a first-line treatment in patients with CRPC. OncoGenex reported that treatment with custirsen did not meet the primary endpoint of statistically significant improvement in overall survival compared to first-line therapy alone (median survival 23.4 months vs. 22.2 months, respectively.) OncoGenex is continuing development of custirsen and has completed enrollment in the Phase 3 AFFINITY study in patients with CRPC and plans to report top-line data from this study in late 2015/early 2016. OncoGenex is also evaluating custirsen in a Phase 3 clinical study, ESPIRIT, as a second-line treatment in patients with NSCLC.

Apatorsen — Apatorsen, formerly OGX-427, is an antisense drug designed to target 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 apatorsen in patients with cancer. In June 2010, OncoGenex reported results from a Phase 1 study of apatorsen in patients with a variety of cancers. In this study, patients treated with apatorsen as a single agent and in combination with docetaxel tolerated the drug well. In addition, apatorsen, when used as a single agent, demonstrated declines in circulating tumor cells at all doses and in all types of cancer OncoGenex evaluated. OncoGenex has also reported results from a Phase 1 study in patients with superficial bladder cancer. In this study, OncoGenex reported that treatment with apatorsen resulted in a trend towards decreased levels of Hsp27 and increased tumor cell death rates.

OncoGenex has initiated a broad Phase 2 program evaluating apatorsen in seven Phase 2 studies in patients with cancer. In September 2012, OncoGenex reported preliminary results from a Phase 2 study in patients with CRPC. In this study, OncoGenex reported that treatment with apatorsen 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.

OncoGenex is evaluating apatorsen in a Phase 2 study, referred to as Borealis-1, in patients with metastatic bladder cancer in combination with first-line gemcitabine and cisplatin. In December 2014, OncoGenex reported top-line data from this study showing that treatment at the 600 mg dose correlated with a 14 percent reduction in risk of death and a 17 percent reduction in progressive disease and death. OncoGenex reported that less benefit was observed in the 1000 mg cohort due to increased adverse events leading to a higher rate of discontinuation of both apatorsen and chemotherapy.

OncoGenex is also evaluating apatorsen in these five Phase 2 studies:

- Borealis-2 is a study in patients with advanced or metastatic bladder cancer in combination with docetaxel. OncoGenex began enrolling in this study in April 2013.
- Pacific is an investigator-sponsored study in combination with Zytiga and prednisone in patients with metastatic CRPC who have PSA progression. Enrollment is estimated to be 80 patients and began in December 2012.
- Spruce is an investigator-sponsored study in combination with carboplatin/pemetrexed therapy in patients with previously untreated Stage IV non-squamous NSCLC. Enrollment is estimated to be 155 patients and began in August 2013.
- Cedar is an investigator-sponsored study in combination with carboplatin/gemcitabine therapy in patients with previously untreated advanced Non-squamous lung cancer. Enrollment is estimated to be 140 patients and began in August 2014.
- Rainier is an investigator-sponsored study in combination with ABRAXANE and gemcitabine therapy in patients with previously untreated metastatic pancreatic cancer. Enrollment is estimated to be 130 patients and began in August 2013.

ISIS-STAT3-2.5$_{Rx}$ — We designed ISIS-STAT3-2.5$_{Rx}$, also called AZD9150 and formerly 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.

ISIS-STAT3-2.5$_{Rx}$ 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-STAT3-2.5$_{Rx}$ broadens the therapeutic opportunities for ISIS-STAT3-2.5$_{Rx}$ into many different types of cancer where STAT3 is implicated.

In preclinical studies, ISIS-STAT3-2.5$_{Rx}$ demonstrated antitumor activity in animal models of human cancer with an attractive safety profile. We reported interim Phase 1 data in patients with cancer who did not adequately respond to prior chemotherapy treatment. In this study, we showed that ISIS-STAT3-2.5$_{Rx}$ treatment resulted in clear responses in patients with advanced cancer with an acceptable safety profile. Based on these data, we initiated a Phase 2 study in focused patient populations with advanced cancer, including patients with advanced lymphomas. We plan to report data from this Phase 2 study at a future scientific meeting.

In 2012, we licensed ISIS-STAT3-2.5$_{Rx}$ to AstraZeneca as part of a broad alliance to discover and develop anti-cancer drugs. AstraZeneca is conducting a Phase 1/2 study of ISIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC, a type of liver cancer. In November 2014 at the European Cancer Symposium, AstraZeneca presented results from this study showing that treatment with ISIS-STAT3-2.5$_{Rx}$ provided evidence of antitumor activity in patients with HCC. In this late-stage population, several patients experienced stable disease and one patient experienced a durable, partial response (78% tumor shrinkage) while on ISIS-STAT3-2.5$_{Rx}$ treatment.

AstraZeneca plans to evaluate ISIS-STAT3-2.5$_{Rx}$ as an immunomodulatory agent in combination with MEDI4736, AstraZeneca's investigational human monoclonal antibody designed to counter tumors' immune evading tactics.

ISIS-AR-2.5$_{Rx}$ — ISIS-AR-2.5$_{Rx}$, also called AZD5312 and formerly ISIS-AZ1$_{Rx}$ and ISIS-AR$_{Rx}$, is an antisense drug we designed to inhibit the production of the androgen receptor, or AR, for the treatment of patients with prostate cancer. Prostate cancer growth, proliferation and progression are all androgen-dependent, and AR function is involved in disease progression at all stages of prostate cancer. For patients diagnosed with metastatic prostate cancer, current treatments largely involve opposing the action of androgens by blocking the androgen receptor or removing circulating androgens. Although androgen deprivation therapy approaches are initially effective in delaying disease progression in patients with metastatic prostate cancer, over time the course of the disease will progress in many of these patients. Resistance to current therapies is frequent and can occur through a variety of mechanisms including the activation of AR signaling in tumor cells through the amplification, over expression and mutation of the AR gene. Because ISIS-AR-2.5$_{Rx}$ can inhibit the production of all known forms of AR, including variants of the AR gene, we believe that this drug has the potential to be an effective treatment for all stages of prostate cancer, including prostate cancer patients who are resistant to current therapies.

In preclinical studies, ISIS-AR-2.5$_{Rx}$ demonstrated antitumor activity in animal models of prostate cancer, including a model resistant to enzalutamide, a small molecule antagonist often used in patients with castration-resistant prostate cancer. In November 2014 at the European Cancer Symposium, AstraZeneca presented preclinical results of ISIS-AR-2.5$_{Rx}$ showing ISIS-AR-2.5$_{Rx}$ can substantially reduce levels of all forms of the androgen receptor, including splice variants that have been implicated in promoting androgen resistance in prostate cancer. Moreover, evidence was presented demonstrating that ISIS-AR-2.5$_{Rx}$ is effective in prostate cancer models that display resistance to current standard of care prostate cancer treatments.

ISIS-AR-2.5$_{Rx}$ is part of our collaboration with AstraZeneca to discover and develop anti-cancer drugs. AstraZeneca is currently evaluating ISIS-AR-2.5$_{Rx}$ in a Phase 1/2 study in patients with AR-related cancers and plans to report data from this study in 2015.

Other Drugs in Development

The broad applicability of our antisense technology allows us to create promising drugs and 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 have licensed 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, such as the ocular and antiviral drugs we and GSK are developing under our preferred partner collaboration.

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 is currently evaluating plazomicin in a Phase 3 study in patients with serious multi-drug resistant, or MDR, gram-negative bacterial infections. The Phase 3 study is designed as a superiority study to evaluate the efficacy and safety of plazomicin compared to colistin in patients with bloodstream infections and nosocomial pneumonia caused by carbapenem-resistant Enterobacteriaceae, or CRE. Achaogen announced last year that it has reached a special protocol assessment, or SPA, with the U.S. Food and Drug Administration for this Phase 3 study.

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 with Excaliard Pharmaceuticals, Inc. and exclusively licensed it to Excaliard for the local treatment of fibrotic diseases, including scarring. Fibrosis represents a significant and expanding area of unmet medical need in which antisense drugs could offer a unique advantage as anti-fibrotic agents. In November 2011, Pfizer Inc. acquired Excaliard. Pfizer has been evaluating EXC 001 in a Phase 2 program designed to provide information, including the optimization of the dose, for the design of the Phase 3 program for EXC 001.

ATL1102 — 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 multiple sclerosis, or MS. We licensed ATL1102 to ATL in December 2001. In 2008, ATL reported Phase 2a results of ATL1102 showing significantly reduced disease activity in patients with relapsing remitting MS. In 2014, ATL completed a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in patients with MS.

RG-101 — RG-101 is a preclinical drug that Regulus is developing. RG-101 is an anti-miR, antisense drug designed to target microRNA-122, or miR-122. Researchers believe that miR-122 is essential for the replication of HCV suggesting that an anti-miR-122 drug may reduce HCV infection and improve HCV-associated pathologies like fatty liver.

MicroRNAs are small RNA molecules that do not encode proteins, but instead work as natural antisense sequences that scientists believe regulate the expression of approximately one-third of all human genes.

In February 2015, Regulus reported data from the Phase 1/2 study of RG-101 in patients with HCV. Regulus reported results from this study demonstrating that treatment with a single subcutaneous dose of 2 mg/kg or 4 mg/kg of RG-101 as monotherapy resulted in significant and sustained reductions in HCV RNA in a varied group of patients, including difficult to treat genotypes and patients who experienced viral relapse after a prior interferon-containing regimen. Additionally, RG-101 was well tolerated and has demonstrated a favorable pharmacokinetic profile to date, which Regulus believes may allow RG-101 to be combined with oral direct-acting antiviral agents to treat HCV. Regulus expects to initiate two Phase 2 studies evaluating RG-101 as a single agent and in combination with direct acting antivirals in patients with HCV in 2015.

ISIS-HBV$_{Rx}$ — ISIS-HBV$_{Rx}$, formerly ISIS-GSK3$_{Rx}$, is an antisense drug we designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection and replication. Hepatitis B virus infection is a serious health problem that can lead to significant and potentially fatal health conditions. Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, including oral antiviral agents or injectable interferons, do not clear HBV and do not effectively clear HBV antigens from these patients. As a result, patients are unable to fully control HBV infection and achieve sustained disease remission. Many of these patients are at elevated risk for severe liver complications such as cirrhosis and primary liver cancer.

In preclinical studies, an antisense compound targeting HBV produced dose-dependent reductions of HBV-associated antigens, including hepatitis B surface antigen, which is present in both acute and chronic infections and is associated with a poor prognosis in patients with chronic HBV infection. In addition, other measures of viral infection were reduced in both the liver and serum following treatment with the ISIS-HBV$_{Rx}$. We have completed a Phase 1 study of ISIS-HBV$_{Rx}$ in healthy volunteers and plan to initiate a Phase 2 study in patients with HBV in 2015.

Preclinical Development

The table below lists our preclinical drugs for a number of different diseases.

Drug	Indication	Partner
ISIS-GSK4-L_{Rx}	Ocular Disease	GSK
ISIS-GSK6-L_{Rx}	Antiviral	GSK

Antisense Technology

Our core technology platform 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 or reduce harmful RNAs without disrupting other proteins that are necessary for the body's normal functions. We are currently pursuing antisense drug discovery programs focused on various severe and rare, cardiovascular, 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 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. We primarily use our antisense technology to interrupt 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 RNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of RNA. These potent antisense drugs inhibit the production of disease-causing proteins or reduce harmful RNAs. Specifically, almost all of our antisense drugs in development cause a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target RNA. 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 RNA through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the target RNA.

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 generally demonstrated enhanced tolerability profiles in numerous 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 is a large unmet medical need. These include diseases that are severe and rare and diseases for which there are limited or no current treatments or in diseases for which we believe our drugs have a competitive advantage over existing therapies. In addition, our research programs focus on the planned advancement of our technology for future antisense drugs. We are designing drugs using our next generation chemistry, generation 2.5, an advancement that we believe increases the potency of our drugs by up to 10-fold and could have the potential to make oral administration commercially feasible. We have published data demonstrating that our generation 2.5 drugs generally have enhanced potency over our generation 2.0 drugs and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland and peripheral nerves. Our generation 2.5 drugs constitute some of our recently added new drugs. We notate in our pipeline which drugs incorporate our generation 2.5 chemistry by appending a 2.5 at the end of the drug name. Currently ISIS-STAT3-2.5$_{Rx}$, ISIS-DMPK-2.5$_{Rx}$, ISIS-AR-2.5$_{Rx}$, and ISIS-RHO-2.5$_{Rx}$ incorporate our generation 2.5 chemistry.

In addition to improving the chemical foundation of our drugs, we have also created a technology suite, LICA, designed to enhance the delivery of our drugs to particular tissues. We believe that our LICA technology could further enhance the potency of our drugs. For example, our LICA technology directed toward liver targets produced a ten-fold increase in potency in preclinical studies in both our second-generation and our generation 2.5 drugs. We currently have eight second generation-LICA drugs in our pipeline, ISIS-AGT-L$_{Rx}$, ISIS-ANGPTL3-L$_{Rx}$, ISIS-APO(a)-L$_{Rx}$, ISIS-APOCIII-L$_{Rx}$, ISIS-GHR-L$_{Rx}$, ISIS-GSK4-L$_{Rx}$, ISIS-GSK6-L$_{Rx}$, and ISIS-TMPRSS6-L$_{Rx}$. All of these drugs are designed to inhibit targets in the liver. We expect that some of our future drugs, including our generation 2.5 drugs, could also be enhanced with our LICA technology.

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 RNA interference, or RNAi, and splicing, and many different RNA targets, including long, non-coding RNAs and toxic RNAs. For example, RNAi is an antisense mechanism that uses small interfering RNA, or siRNA, that exploits 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 or drug delivery vehicles to achieve delivery to the cell. 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 mechanisms, 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 SMN1 gene leading to a decrease in the protein 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. In 2014, we reported encouraging data on ISIS-SMN_{Rx} in both infants and children with SMA. ISIS-SMN_{Rx} is currently being evaluated in two Phase 3 studies in infants and children with SMA. There are a number of diseases, including cystic fibrosis and Duchenne muscular dystrophy, which scientists believe are splicing disorders. These are diseases we could potentially treat using antisense modulation of splicing.

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 believe that we can apply the principles of our technology to develop drugs that target other non-coding RNAs, such as toxic RNAs. For example, DM1 is a form of muscular dystrophy that is caused by an abnormally long, toxic RNA that accumulates in cells and prevents the production of proteins essential for normal cellular function. We designed our drug, ISIS-DMPK-2.5_{Rx}, to target and reduce the toxic RNA. In our preclinical studies, we observed effective reductions of the toxic RNA that led to a reversal of disease symptoms that was sustained for up to one year in a mouse model of disease. In December 2014, we initiated a clinical study evaluating ISIS-DMPK-2.5_{Rx} in patients with DM1.

Another RNA target for our antisense technology is 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. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam Pharmaceuticals, Inc. established Regulus as a company focused on the discovery, development and commercialization of microRNA-based therapeutics. In 2014, Regulus reported human proof-of-concept with RG-101 in HCV patients demonstrating that treatment with a single subcutaneous dose of RG-101 as a single agent resulted in significant and sustained reductions in HCV RNA in a varied group of patients, including difficult to treat genotypes and patients.

We are also making progress on developing antisense drugs that are designed to target long, non-coding RNAs. In 2014, we published a paper in Nature in which we were the first to show that targeted reduction of a long non-coding RNA with an antisense compound can ameliorate certain cognitive deficits in a mouse model of angleman syndrome, or AS. Moreover, these studies demonstrate the potential therapeutic benefits of an antisense compound for the treatment of AS.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

To maximize the value of our drugs and technologies, we have employed a multifaceted business and partnering strategy, which has included a range of approaches to developing and commercializing products. Our partnering strategy has allowed us to build a development pipeline of 38 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 our and our partners' pipelines. In 2014, we formed Akcea, and began the next phase of our business strategy, to develop and commercialize the drugs from our lipid franchise.

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 with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Our partnering strategy provides us the flexibility to license each of our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. Using this strategy, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. Just as we have advanced and matured our technology and pipeline, we have evolved our partnering strategy in order to maximize the value of each of our assets. We have a multifaceted partnering strategy that we employ; partnering certain research programs or drugs early, partnering drugs after we have completed proof-of-concept, and partnering drugs that we have advanced into later stages of development.

Preferred Partner Transactions

We form preferred partner transactions for certain therapeutic programs where a partner brings expertise that we do not have in house and that could provide us with an increased likelihood of successfully bringing the program to market. Typically these collaborations are focused on drugs in therapeutic areas of high risk, like severe neurological diseases, or in areas in which Phase 2 results would likely not provide a significant increase in value, like cancer. For these programs, we partner early, occasionally prior to clinical development. In this way, we have a vested partner, such as with AstraZeneca, Biogen Idec, GSK, Janssen Pharmaceuticals and Roche, early in the development of a drug. Typically, these preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. As in our other partnerships, we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

Traditional Alliances

We form traditional partnering alliances that enable us to discover and conduct early development for drugs in our pipeline that we feel could address large patient populations or multiple indications. For these drugs, late-stage development is often costly and requires complex Phase 3 development programs. In this strategy, we are responsible for clinical development to proof-of-concept, at which time we outlicense our drugs to partners, such as when we licensed KYNAMRO to Genzyme, and build a broad base of license fees, milestone payments, profit share and royalty income. For example, we have a broad portfolio of drugs to treat type 2 diabetes. Because late-stage clinical development for type 2 diabetes can be large and expensive, we will seek a partner to license these drugs and to conduct late-stage clinical development and commercialization. With the potentially competitive benefit of our drugs over existing therapies and clinical proof-of-concept data, we believe that we could license our type 2 diabetes drugs.

Captive Development & Commercialization Company; Akcea Therapeutics

And finally, we have evolved our business strategy to retain greater control over the development of our drugs and retain a larger portion of the commercial revenue. For these drugs, we believe that we have a clear and relatively quick path to the market, such as with drugs for rare disease opportunities. These drugs have clearly defined patient populations with minimal or no available treatments. Many of the drugs in our pipeline that meet these criteria are part of our lipid franchise. In late 2014, we established a wholly owned subsidiary, Akcea Therapeutics, Inc., to develop and commercialize the drugs from our lipid franchise. Akcea is focused on developing ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$, plus more potent follow on drugs for these programs. We hired a senior business leader with commercialization expertise in severe and rare and cardiovascular diseases to lead Akcea and to maximize the value of our lipid franchise assets. Moving our lipid assets into a company that we own and control keeps our core focus at Isis on innovation and allows us to maintain control over and retain more value from our lipid drugs.

Satellite Companies

We also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We call these companies satellite companies. 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. We also benefit from our ownership in these satellite companies.For example, Regulus is a satellite company partner that we co-founded to discover and develop antisense drugs targeting microRNAs. In 2014, we sold a portion of our shares in Regulus for more than $20 million of cash, and we remain a significant shareholder in the company.

In addition to our satellite company drug development partners, we form satellite company partnerships focused on developing and advancing certain RNA-targeting therapeutic technologies. These partnerships take advantage of our dominant RNA-targeting 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. We provide more information on our satellite company partners in this section under the subheading "Satellite Company Collaborations".

We highlight our traditional pharmaceutical and satellite company partnerships below. In addition, we have numerous other partnerships, which we also describe below.

Preferred Partner Transactions & Traditional Alliances

We have a long 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, profit share and royalty income. In contrast, our preferred partner transactions provide us with a vested partner early in the development of a drug. With our preferred partners, we are able 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 established a broad strategic alliance with Biogen Idec that pairs Biogen Idec's extensive resources and expertise in neurological diseases with our antisense technology. Together we are creating a franchise of novel treatments for neurological disorders that will expand both our pipeline and Biogen Idec's pipeline with promising new treatments. In cancer, we are working with our partner, AstraZeneca, to conduct comprehensive clinical programs for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$, anti-cancer drugs 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 December 2014, we entered into a preferred partner transaction with Janssen. Together with Janssen, we plan to expand the reach of our antisense technology to discover and develop antisense drugs to treat autoimmune disorders of the GI tract.

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 ourselves through proof-of-value 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 collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under a separate research program. Together with AstraZeneca, we are evaluating ISIS-STAT3-2.5$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a clinical study of ISIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic HCC. We are conducting a clinical study evaluating ISIS-STAT3-2.5$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$. In June 2013, we and AstraZeneca added a second development candidate, ISIS-AR-2.5$_{Rx}$, to our collaboration. ISIS-AR-2.5$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of AR. AstraZeneca is currently evaluating ISIS-AR-2.5$_{Rx}$ in a Phase 1/2 study in patients with AR-related cancers. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-AR-2.5$_{Rx}$. In addition, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities for such drug.

Under the terms of the agreement, we received $31 million comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013. We recorded revenue of $11.5 million upon receipt of these payments. We are recognizing the remaining $19.5 million into revenue as follows:

- $11.2 million related to the ISIS-AR-2.5$_{Rx}$ program, which we amortized through March 2014;
- $7.6 million related to the option to license three drugs under a separate research program, which we are amortizing through December 2016; and
- $0.7 million related to the ISIS-STAT3-2.5$_{Rx}$ program, which we amortized through February 2015.

In June 2014, we earned a $15 million milestone payment when AstraZeneca initiated a Phase 1 study of ISIS-AR-2.5$_{Rx}$. From inception through February 2015, we have earned $25 million in milestone payments related to the development of ISIS-AR-2.5$_{Rx}$.

In October 2014, we and AstraZeneca amended our agreement for ISIS-STAT3-2.5$_{Rx}$. Under the amended terms of the agreement, we received a $7.5 million milestone payment in November 2014 from AstraZeneca for advancing ISIS-STAT3-2.5$_{Rx}$ in patients with advanced cancers. We recognized into revenue $7.1 million of the $7.5 million milestone payment when we received the payment in November 2014 and we amortized the remaining balance through February 2015. Upon AstraZeneca's initiation of a Phase 2 study, we will earn a $17.5 million milestone payment.

We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive royalties up to the low to mid-teens on any product sales of drugs resulting from this collaboration. If AstraZeneca successfully develops ISIS-STAT3-2.5$_{Rx}$, ISIS-AR-2.5$_{Rx}$, and the three drugs under the research program, we could receive milestone payments of more than $858 million, including up to $238 million for the achievement of development milestones and up to $620 million for the achievement of regulatory milestones. We will earn the next milestone payment of $10 million if we designate a development candidate for a cancer drug under our research program with AstraZeneca.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration. If AstraZeneca exercises its option, it will be responsible for all further global development, regulatory and commercialization activities for such drug. We received a $0.8 million upfront payment, which we are amortizing through December 2016. We are eligible to receive license fees and milestone payments of $163.2 million, including up to $45.3 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.3 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Our agreement with AstraZeneca will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012 we earned revenue of $27.7 million, $29.1 million and $9.3 million, respectively, from our relationship with AstraZeneca, which represented 13 percent, 20 percent and nine percent, respectively, of our total revenue for those periods.

Biogen Idec

We have established four strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise for neurological disorders.

ISIS-SMN$_{Rx}$

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We are currently conducting a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. In addition, we are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation study in infants with SMA. Patients from both of the Phase 2 studies continue to have access to ISIS-SMN$_{Rx}$ through open-label extension dosing. We are responsible for completing the Phase 2 and Phase 3 trials we are currently conducting. If Biogen Idec exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen Idec has the option to license ISIS-SMN$_{Rx}$. Biogen Idec may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA.

We received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. In 2014, we and Biogen Idec amended our original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. As a result, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by approximately $57 million. Under the terms of the amended agreement, we are eligible to receive up to $327 million in a license fee and payments, including $102.2 million in milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. We will earn the next milestone payment of $9 million if we further advance the Phase 3 study in infants with SMA.

In 2014, we earned an $18 million milestone payment when we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and we earned a $27 million milestone payment when we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. From inception through February 2015, we have earned $71.3 million in payments for advancing ISIS-SMN$_{Rx}$. We are amortizing a portion of those payments as follows:

- $3.8 million related to the Phase 2 studies in children and infants with SMA, which we amortized through July 2014; and
- $7.5 million related to an open-label extension study in children with SMA, which we are amortizing through March 2015.

ISIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen Idec entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, ISIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the first Phase 2 trial. If Biogen Idec exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and milestone payments, including up to $59 million in development milestone payments and $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of the drug. From inception through February 2015, we have earned $24 million in milestone payments associated with the clinical development of ISIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $35 million if we initiate a Phase 2 study for ISIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen Idec has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. If Biogen Idec exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and milestone payments per program. We are eligible to receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials. We are also eligible to receive up to $130 million in milestone payments per program if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of drugs resulting from each of the three programs. In February 2015, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study of ISIS-BIIB4$_{Rx}$, a drug for an undisclosed target designed to treat a neurodegenerative disease. We will earn the next milestone payment of up to $14 million if we initiate a Phase 1 study for ISIS-BIIB4$_{Rx}$.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration agreement, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. If Biogen Idec exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive single-digit royalties on any product sales of drugs using non-antisense modalities developed under this collaboration. Through February 2015, we have earned $25 million in milestone payments related to advancing three different targets under this collaboration. We will earn the next milestone payment of up to $10 million if we choose another target to advance under this collaboration.

Each of our agreements with Biogen Idec will continue until the earlier of the date all of Biogen Idec's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen Idec exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen Idec may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen Idec may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen Idec may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen Idec may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012, we earned revenue of $123.2 million, $37.0 million and $8.5 million, respectively, from our relationship with Biogen Idec, which represented 58 percent, 25 percent and eight percent, respectively, of our total revenue for those periods.

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 47 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. From inception through February 2015, we have earned $50 million in milestone payments for advancing KYNAMRO in development. We may also receive over $1.5 billion in regulatory and commercialization milestone payments.

Under our alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. Genzyme is marketing KYNAMRO in the United States for patients with HoFH and has also obtained marketing approval in other countries, including Mexico, Argentina, South Korea and Peru, and is pursuing marketing approval in multiple additional markets. 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 are sharing development expenses equally until 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.

During 2013 and 2012, we earned revenue of $32.5 million, and $67.6 million, respectively, from our relationship with Genzyme, which represented 22 percent and 66 percent, respectively, of our total revenue for those years. During 2014, we did not earn any revenue from our relationship with Genzyme.

GSK

In March 2010, we entered into a strategic alliance with GSK using 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. Our strategic alliance currently includes five drugs in development. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when we and GSK expanded the collaboration.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. From inception through February 2015, we have received $45 million, primarily in milestone payments, from GSK related to the development of ISIS-TTR_{Rx}. We are also eligible to earn an additional $25 million in pre-licensing milestone payments associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} receive marketing approval and meet pre-agreed sales targets.

In addition to ISIS-TTR_{Rx}, we have four drugs in development. We are developing ISIS-HBV_{Rx}, an antisense drug designed to reduce the production of viral proteins associated with HBV infection. We are also developing ISIS-GSK4-L_{Rx} and ISIS-RHO-2.5$_{Rx}$, formerly ISIS-GSK5$_{Rx}$, which are antisense drugs we designed to treat ocular diseases. In addition, we recently advanced a drug to treat an undisclosed target, ISIS-GSK6-L_{Rx}, into development.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and milestone payments of more than $1.2 billion, including up to $146.5 million for the achievement of development milestones, up to $483.5 million for the achievement of regulatory milestones and up to $428 million for the achievement of commercialization milestones. We will earn the next $15 million milestone payment if we further advance ISIS-TTR_{Rx}. In addition, we are eligible to receive royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the ISIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the ISIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012, we earned revenue of $37.3 million, $35.3 million and $8.2 million, respectively, from our relationship with GSK, which represented 17 percent, 24 percent and eight percent, respectively, of our total revenue for those years.

Janssen Biotech, Inc., a pharmaceutical company of Johnson & Johnson

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in payments, made up of a $30 million payment we received in December 2014 and a $5 million payment we received in February 2015. We are amortizing these payments through December 2018. We are eligible to receive nearly $800 million in milestone payments and license fees for these programs, including up to $175 million for the achievement of development milestones, up to $420 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the near teens on any product sales of drugs resulting from this collaboration. We will earn the next milestone payment of $5 million if Janssen chooses another target to advance under this collaboration.

Our agreement with Janssen will continue until the earlier of the date that all of Janssen's options to obtain the exclusive licenses under the agreement expire unexercised or, if Janssen exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Janssen may terminate the agreement or any program at any time by providing written notice to us; and
- Either we or Janssen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012 we did not earn any revenue from our relationship with Janssen.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting HTT protein. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestone payments. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us;
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent; and
- Either we or Roche may terminate the brain shuttle program if at least one development candidate is not designated under such program by a mutually agreed deadline.

During 2014 and 2013, we earned revenue of $8.7 million and $5.1 million, respectively from our relationship with Roche.

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 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. For example, we co-founded Regulus, a company focused on developing microRNA-targeted therapeutics in cancer, fibrosis, atherosclerosis and viral infections, such as HCV. Regulus has developed strategic alliances with high-quality partners such as Sanofi, Biogen Idec and AstraZeneca, from which we have the potential to receive a portion of future milestone payments and/or royalty payments under our agreement with Regulus. In 2014 and 2015, Regulus reported positive results on RG-101, Regulus' first anti-miR drug in clinical development.

The value of our satellite company strategy is evident in the broad pipeline of drugs we and our partners are developing to treat a wide range of diseases. Using their resources and their expertise, our partners are instrumental in developing 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 satellite company partner incurs the cost of development and assumes the risk.

In addition to our satellite company partners that are advancing RNA-targeting therapeutics, we have satellite company partners who take advantage of our dominant RNA-targeting 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.

Achaogen, Inc.

In 2006, we exclusively licensed 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. Plazomicin 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 earned $7 million in milestone payments from Achaogen, including a $4 million milestone payment we earned in September 2014 when Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $42.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $7.5 million if Achaogen obtains regulatory approval for plazomicin in a major market. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

During 2014 we earned $4 million in revenue from our relationship with Achaogen. During 2013 and 2012, we did not earn any revenue from our relationship with Achaogen. During 2014, we sold all of the Achaogen stock we owned resulting in net proceeds of $1.3 million.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize 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 from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include double-stranded RNAi technology for agricultural products.

For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In December 2014, we earned a $0.4 million milestone payment from Alnylam for the initiation of a Phase 1 study. We will earn the next milestone payment of $0.4 million if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We also have the potential to earn a portion of payments that Alnylam receives from licenses of our technology it grants to its partners plus royalties. Through February 2015, we have earned a total of $50.8 million from Alnylam resulting from licenses of our technology Alnylam has granted to its partners, including $9.5 million we earned in 2014. 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 single-stranded antisense therapeutics, or 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 up to $3.4 million in milestone payments for specified development and regulatory events plus royalties. To date, we do 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 January 2015, we and Alnylam entered into a new alliance in which we formed an intellectual property cross-license with reciprocal economic terms on four therapeutic targets. Under the terms of the agreement, we and Alnylam each obtained exclusive license rights to two therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA-targeting mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets, Factor XI and Apo(a). In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA-targeting mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets, antithrombin and aminolevulinic acid synthase-1. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics.

During 2014, 2013 and 2012, we earned revenue from our relationship with Alnylam totaling $9.9 million, $1.5 million and $2.7 million, respectively.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is developing ATL1102 for the treatment of multiple sclerosis. In addition, ATL is currently developing ATL1103 for growth and sight disorders. 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, 2014 and 2013, we owned less than 10 percent of ATL's equity. During 2014, 2013 and 2012, we did not earn any revenue 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.

Under the agreement, we could receive 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 $0.6 million if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for patients with IBD for which we receive royalties.

In 2010 and 2013, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we agreed to receive equity for the royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of value from the equity is uncertain. At December 31, 2014 and 2013, we owned approximately 12 percent of Atlantic Pharmaceuticals' equity. We earned $0.7 million related to royalties and sales of drug substance in 2013. Because the payments were made in equity, we did not record any revenue. During 2014 and 2012, our revenue was negligible 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 $6.5 million in contingent payments from Pfizer 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, if Pfizer Inc. successfully develops and commercializes EXC 001, we may receive 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 also eligible to receive royalties on any product sales of EXC 001.

At December 31, 2014, we owned no equity in Excaliard. During 2013 and 2012, we received $0.8 million and $1.3 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard and for advancing of EXC 001, which we recorded as investment gains. We did not earn any revenue during 2014, 2013 and 2012 from our relationship with Excaliard.

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

Custirsen, formerly OGX-011

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, 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 core antisense technology patents we licensed to OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026, its foreign equivalents granted in Australia and Canada, and its foreign equivalent pending under the European Patent Convention. 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. OncoGenex recently announced that it executed an initial agreement with Teva to regain rights to custirsen.

OGX-225

In August 2003, we and OncoGenex entered into a second and separate agreement for the development of an 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 $0.8 million of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us 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, 2014, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $0.5 million if OncoGenex initiates a Phase 2 study for OGX-225.

Apatorsen, formerly OGX-427

In January 2005, we entered into a third and separate agreement with OncoGenex to allow for the development of an additional antisense anti-cancer drug, apatorsen. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex will pay us 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. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for apatorsen.

During 2014, 2013 and 2012, 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. 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, atherosclerosis and viral infections, such as HCV, and currently has two drugs in development. Regulus is developing RG-101, an anti-miR that targets microRNA-122, for the treatment of HCV infection. Regulus is also developing RG-012, an anti-miR that targets microRNA-21, for the treatment of Alport Syndrome. We are eligible to receive royalties on any future product sales of both of these drugs.

Regulus has strategic partnerships with Sanofi, Biogen Idec and AstraZeneca. We benefit from Regulus' strategic partnerships because we have the potential to receive a portion of upfront payments, future milestone payments, and/or royalty payments. For example, under Regulus' strategic partnership with Sanofi, and as a result of our agreement with Regulus, we received 7.5 percent, or $1.9 million, of the $25 million upfront payment.

During 2014, 2013 and 2012, we did not earn any revenue from our relationship with Regulus. During 2014, we sold a portion of our Regulus stock, resulting in a $19.9 million gain and proceeds of $22.9 million. As of December 31, 2014, we remain a significant shareholder with approximately 5.5 million shares, approximately 11 percent of Regulus' equity, with a net carrying value of $81.9 million.

External Project Funding

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

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. In 2013, we made two payments to CHDI totaling $3 million associated with the progression of our Huntington's disease program, which we recorded as research and development expense. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI. During 2013 and 2012, we earned revenue of $0.4 million and $2.0 million, respectively, from our relationship with CHDI. During 2014, 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.

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. To date, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Sales of Intellectual Property

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, we are eligible to receive earn out payments from AMI equal to a percentage of Ibis' revenue related to sales of Ibis systems, which AMI launched in 2014 as IRIDICA, including instruments, assay kits and successor products. Once cumulative net sales reach $140 million, and through December 31, 2025, we are eligible to earn out payments in any year that net sales exceed $50 million for the applicable year. 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 2014, 2013 and 2012, we did not earn any revenue from our relationship with AMI.

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.

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 a milestone payment to the University of Massachusetts of $0.3 million for the achievement of a key regulatory milestone. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive in consideration for 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 a milestone payment of $0.5 million to the Cold Spring Harbor Laboratory for the achievement of a key regulatory milestone. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue and post licensing milestone payments up to $11.3 million we receive in consideration for 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.

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. Our drug substance manufacturing facility is located in a 28,700 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 a 25,800 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. Our manufacturing facility is subject to periodic inspections by the FDA to ensure that it is operating in compliance with current Good Manufacturing Practices, or cGMP, requirements.

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, AstraZeneca, Biogen Idec, Bristol-Myers Squibb, Eli Lilly and Company, Genzyme, iCo, OncoGenex and Ortho-McNeil-Janssen Pharmaceuticals, Inc.

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 to meet our current internal research and clinical needs, including for the Phase 3 clinical trials for ISIS-TTR$_{Rx}$, ISIS-SMN$_{Rx}$, and ISIS-APOCIII$_{Rx}$. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs, including the initial launch supplies for ISIS-TTR$_{Rx}$, ISIS- SMN$_{Rx}$, and ISIS-APOCIII$_{Rx}$. 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.

In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. We provided the drug substance necessary for the initial launch of KYNAMRO and Genzyme is responsible for the long-term supply of KYNAMRO drug substance. Genzyme manufactures the finished drug product for KYNAMRO and is offering KYNAMRO in the United States and other specific countries in pre-filled syringes. Genzyme is producing the pre-filled syringes using one of its own manufacturing facilities.

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 10, 2015, we owned or exclusively licensed more than 1,300 issued patents worldwide. We focus our resources on patents and new patent applications that drive value for our company.

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 to specifically protect each of our drugs. For example, 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**
	Broadly Applicable	
Chemically Modified Nucleosides and Oligonucleotides		Target and sequence independent
Antisense Drug Design Motifs		Sequence independent
Therapeutic Methods		Chemistry independent
Antisense Sequence		Specific claim to drug candidates
Drug Composition		
	Specific	

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 generation 2.5 compounds, the constrained-ethyl nucleosides, or cEt, nucleosides. In June 2011, Santaris Pharma A/S opposed our granted patent in Europe drawn to cEt containing nucleotides and oligonucleotides and we intend to vigorously defend our patent in these proceedings. Further information about litigation with Santaris can be found in Item 3, *Legal Proceedings.*

The following are some of our patents in this category:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'O-MODIFIED PURINES	2023	Covers certain MOE nucleosides and oligonucleotides containing said nucleotides.
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers methods of synthesizing our cEt nucleosides.
Europe	EP1984381	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 ribonuclease H, or 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 gapmer antisense drugs until March of 2023. We also have issued patents covering other gapmer drug designs, and methods of lowering a target RNA in an animal with these gapmer compositions. The following patent is one example of our patents in this category.

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
United States	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	Covers 2'-O-alkyl-O-alkyl gapmer oligonucleotides.

Bicyclic Nucleoside Gapmer Oligonucleotides

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

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
Europe	EP2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes cEt locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders
United States	7,750,131	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers cEt containing gapmer compounds
Europe	EP2092065	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-MOE and bicyclic nucleosides

Therapeutic Methods of Treatment and Antisense Drug Sequences

In addition to our broad core patents, we also own hundreds of 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, India, Japan and 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. 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
United States	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
United States	7,511,131	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2025	Antisense sequence and composition of matter of KYNAMRO
Europe	EP1569695	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
Europe	EP2336318	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
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
Japan	4986109	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO

Apolipoprotein C-III and ISIS-APOCIII$_{Rx}$

We have obtained patent claims in the United States drawn to the use of antisense compounds complementary to a broad active region of human Apo C-III including the site targeted by ISIS-APOCIII$_{Rx}$. Similar claims complementary to any site on human Apo C-III have granted in Australia. We obtained issued patent claims to the specific antisense sequence and chemical composition of ISIS-APOCIII$_{Rx}$ in the United States, Australia, and Europe. The issued U.S. claims should protect ISIS-APOCIII$_{Rx}$ from generic competition in the United States until at least 2023. In addition, we will seek additional patent term extension to recapture a portion of the term lost during FDA regulatory review, extending the term of this patent beyond 2023. We are also pursuing additional patent applications designed to protect the ISIS-APOCIII$_{Rx}$ composition in Canada and additional methods of use in jurisdictions worldwide. The table below lists the key U.S, European and Australian issued patents:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,598,227	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Methods of treating hyperlipidemia, lowering cholesterol levels and lowering triglyceride levels with an antisense compound comprising an antisense oligonucleotide 15-30 linked nucleosides specifically hybridizable within nucleotides 3253-3558 of SEQ ID 4 (apoCIII)
United States	7,750,141	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of ISIS-APOCIII$_{Rx}$
Europe	EP1622597	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of ISIS-APOCIII$_{RX}$
Australia	2004231550	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Compounds 12-50 nucleobases in length specifically hybridizable with SEQ ID 4 (apoCIII), the antisense sequence and chemistry of *ISIS-APOCIII$_{Rx}$* and methods of their use in treating hyperlipidemia, lowering cholesterol levels and lowering triglyceride levels

Survival Motor Neuron and ISIS-SMN$_{Rx}$

ISIS-SMN$_{Rx}$ is protected by a suite of patents in the United States and in Europe from generic competition in the United States until at least 2030 and in Europe until 2026. These issued patents include: (i) the Bennett patent related to methods of altering mRNA processing (i.e., splicing) with a fully-modified 2'MOE oligonucleotide, (ii) a patent licensed from the University of Massachusetts drawn to antisense compounds having the sequence of ISIS-SMN$_{Rx}$, independent of chemical modification and uses of such compounds for treating SMA, and (iii) a joint patent with Cold Spring Harbor Laboratory claiming fully-modified 2'MOE compositions targeting SMN2, including the precise composition of matter of ISIS-SMN$_{Rx}$. Those patents should protect ISIS-SMN$_{Rx}$ from generic and antisense innovator competition in the United States until at least 2030 without patent term extension. The table below lists the key U.S. and European issued patents protecting ISIS-SMN$_{Rx}$:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	6,210,892	ALTERATION OF CELLULAR BEHAVIOR BY MODULATION OF MRNA PROCESSING	2018	Broad claims of altering mRNA processing with a fully-modified 2'MOE oligonucleotide.
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of ISIS-SMN_{Rx}
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of ISIS-SMN_{Rx}
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of ISIS-SMN_{Rx} (chemistry independent)
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of SMN_{Rx} to alter splicing of SMN2 and/or to treat SMA

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, including Europe and Japan. The table below lists the current issued U.S. patents protecting ISIS-TTR_{Rx}:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,101,743	MODULATION OF TRANSTHYRETIN EXPRESSION	2025	Antisense sequence and chemistry of ISIS-TTR_{Rx}
United States	8,697,860	DIAGNOSIS AND TREATMENT OF DISEASE	2031	Composition 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
United States	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.
United States	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.
United States	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.
United States	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.
United States	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.
United States	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.

Custirsen

Issued patent 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
United States	6,900,187	TRPM-2 ANTISENSE THERAPY USING AN OLIOGNUCLEOTIDE HAVING 2'-O-(2-METHOXY)ETHYL MODIFICATIONS	2021	Antisense sequence and composition of custirsen

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. 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.

Our operations may be directly, or indirectly through our customers, distributors, or other business partners, subject to various federal and state fraud and abuse laws, including, without limitation, anti-kickback statutes and false claims statutes. These laws may impact, among other things, our commercialization partners' proposed sales, marketing and education programs.

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits certain individuals and entities, including us, from promising, paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, directly or indirectly, to obtain or retain business or an improper advantage. Violations of the FCPA may result in large civil and criminal penalties and could result in an adverse effect on a company's reputation, operations, and financial condition. A company may also face collateral consequences such as debarment and the loss of export privileges.

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 some 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 has also obtained marketing approval in other countries, including Mexico, Argentina, South Korea and Peru, and is pursuing marketing approval for KYNAMRO in other countries. Apheresis and maximally tolerated lipid-lowering therapies, including statins, have been 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 lomitapide. Lomitapide is a small molecule drug that Aegerion Pharmaceuticals developed and is commercializing to limit secretion of cholesterol and triglycerides from the intestines and the liver. The FDA and EMA have approved lomitapide as an oral, once-a-day treatment for patients with HoFH. The FDA approval for lomitapide is supported by a Phase 3 study in 29 patients with HoFH. 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 lomitapide, patients discontinued use of lomitapide 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 lomitapide. Like KYNAMRO, lomitapide is available only through a REMS program that restricts the access of lomitapide to only patients with a clinical or laboratory diagnosis consistent with HoFH and both the KYNAMRO and lomitapide 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. Patients administer KYNAMRO by injection once weekly at home with a prefilled syringe while patients take lomitapide orally once daily. To avoid gastrointestinal events, patients on lomitapide 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 lomitapide label, concurrent use of lomitapide 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 or diet restrictions, 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, as 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 in excess of $300,000 for lomitapide per patient per year, which is higher than KYNAMRO. Our partner, Genzyme, a Sanofi Company, 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, we believe that Sanofi and its global presence will aid in the expansion of KYNAMRO into markets throughout the world.

ISIS-TTR$_{Rx}$

In February 2013, we began a Phase 3 study evaluating ISIS-TTR$_{Rx}$ in patients with FAP, a severe and rare disease. Patients with FAP have very limited therapeutic options and liver transplantation is the most common treatment used to reduce the production of the plaque-causing protein. Liver transplantation is a very complicated and expensive medical procedure performed only in major medical centers. Patients who receive a liver transplant are often required to take immunosuppressive drugs for the rest of their lives. In addition, due to the previous accumulation of plaques in nerve and heart muscle, normal TTR protein from a normal liver can still aggregate and progress the disease.

We believe that of the drugs that are in development or on the market, ISIS-TTR$_{Rx}$'s closest competitor is patisiran, an intravenously administered RNAi molecule being developed by Alnylam. Patisiran is also designed to inhibit the production of TTR protein by reducing TTR mRNA. As such, patisiran and ISIS-TTR$_{Rx}$ are designed to employ similar mechanisms of action to reduce the disease-causing TTR protein accumulation. In early clinical studies, both drugs produced similar TTR mRNA reduction in treated subjects. In November 2013, Alnylam started APOLLO, a Phase 3 program in patients with FAP. We believe that because we initiated the Phase 3 study for ISIS-TTR$_{Rx}$ approximately ten months earlier than the APOLLO study, ISIS-TTR$_{Rx}$ will be the first RNA-targeted drug on the market. If Alnylam's drug candidate is successful in clinical studies and receives marketing approval, it could compete with ISIS-TTR$_{Rx}$. Tafamadis, an oral drug approved and launched in Europe, Japan and Argentina and approved in Mexico under the brand name Vyndaqel, is another competitor to ISIS-TTR$_{Rx}$. In May 2012, the FDA rejected tafamadis for use in the United States stating that the Phase 3 study data did not show that tafamadis is effective in directly slowing the progression of FAP. We believe that based on the mechanism of our drug and our preclinical data, that ISIS-TTR$_{Rx}$ could have a significantly better therapeutic profile than tafamadis and other drugs that are earlier in development. Another oral drug, diflunisal, has been shown to stabilize the TTR tetramer structure and could also offer benefit to patients with TTR amyloidosis. Diflunisal is an oral generic drug that is available in the United States and Europe for use as a non-steroidal anti-inflammatory drug. Diflunisal was tested in a Phase 3 study in patients with FAP. In this study more than half of the patients discontinued treatment and although a clinically meaningful change in disease progression was measured, all patients continued to progress in their disease. If diflunisal is successful in receiving marketing approval for TTR amyloidosis, or if prescribed to TTR patients, it could compete with ISIS-TTR$_{Rx}$.

ISIS-APOCIII$_{Rx}$

We have completed a broad Phase 2 program on our novel triglyceride-lowering drug, ISIS-APOCIII$_{Rx}$, and we initiated a Phase 3 program on this drug in the third quarter of 2014. Based on our Phase 2 data, we believe that ISIS-APOCIII$_{Rx}$ will work equally well as a single agent or in combination with other triglyceride-lowering drugs on the market. As such, we do not intend to displace any existing therapy with ISIS-APOCIII$_{Rx}$.

We believe that of the drugs that are in development or on the market, ISIS-APOCIII$_{Rx}$'s closest competitor is the gene therapy treatment Glybera, which is only marketed in Europe. As of December 31, 2014, Glybera had not been approved by the FDA. Glybera was approved by the European Commission in October 2012 as a treatment for adult patients diagnosed with familial lipoprotein lipase deficiency, or LPLD, confirmed by genetic testing, and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. Glybera is being marketed by Chiesi, a partner of UniQure. The European Commission approval was supported by three interventional clinical studies in 27 patients with LPLD. Glybera was well tolerated in these studies, with no relevant safety issues observed. Results of these studies indicated that a single dose administration of Glybera resulted in long-term biological activity of the LPL protein. Chiesi announced that they are seeking a retail price of EUR 53,000 ($65,625) per vial, or about EUR 1.1 million ($1.4 million) per year for Glybera for a patient weighing 62.5kg. This makes Glybera the most expensive rare disease drug in the world. If approved in Europe, ISIS-APOCIII$_{Rx}$ could compete with Glybera in the European Union and if Glybera is successful in obtaining marketing approval in the United States, it could compete with ISIS-APOCIII$_{Rx}$ in the United States. Another potential competitor to ISIS-APOCIII$_{Rx}$ is pradigastat, a drug in Phase 3 development in patients with FCS. If pradigastat is successful in clinical studies and receives marketing approval this oral drug could compete with ISIS-APOCIII$_{Rx}$. Data from a Phase 2 study of pradigastat showed effective lowering of triglycerides in patients, but the high incidence of gastrointestinal side effects observed could limit the drugs' tolerability. Another potential oral drug competitor is CAT-2003, which is in Phase 2 development to treat patients with FCS, or extremely high triglycerides. Based on the mechanism of action of CAT-2003, we believe CAT-2003 is likely to have an effect only in a small subset of FCS patients.

ISIS-SMN$_{Rx}$

In 2014, we initiated two Phase 3 programs on ISIS-SMN$_{Rx}$ in infants and in children with SMA. SMA is a rare genetic disease for which there is no approved therapy on the market. Patients with SMA are treated with palliative care that focuses on helping to maintain respiratory health. We plan to develop ISIS-SMN$_{Rx}$ to treat all forms of SMA. We believe that of the drugs that are in development, ISIS-SMN$_{Rx}$'s closest competitor is RG7800. RG7800 is a small molecule gene splicing modifier that PTC Therapeutics is co-developing with Roche and the SMA Foundation. In November 2014, PTC Therapeutics announced that it initiated a Phase 1b/2a study of RG7800 in adults and pediatric patients with SMA. Another oral drug, olesoxime, has shown beneficial effect on the maintenance of motor function in SMA patients. Roche announced in January 2015 that it plans to acquire Trophos, the company developing olesoxime, which could allow Roche to utilize a single marketing and commercial salesforce for both RG7800 and olesoxime, should both drugs reach the market. Trophos reported that SMA patients treated with olesoxime had less severe loss of motor function compared to patients treated with placebo. AveXis is developing ChariSMA, a gene therapy in Phase 1 development to treat infants with SMA. The first patient was dosed in December 2014. Because chariSMA is the first gene therapy trial for the treatment of patients with SMA and it has just initiated clinical trials, the therapeutic potential of this treatment is difficult to assess. To compete with ISIS-SMN$_{Rx}$ these therapeutic programs would need to advance into Phase 3 studies, eventually achieve marketing approval, and show a better product profile than ISIS-SMN$_{Rx}$. If these programs progress through clinical studies and the resulting drugs receive marketing approval, these drugs could compete with ISIS-SMN$_{Rx}$ as a treatment for patients with SMA.

Employees

As of February 17, 2015, we employed 390 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 17, 2015:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	69	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D.	60	Director, Chief Operating Officer and Secretary
C. Frank Bennett, Ph.D.	58	Senior Vice President, Antisense Research
Sarah Boyce	43	Chief Business Officer
Richard S. Geary, Ph.D.	57	Senior Vice President, Development
Elizabeth L. Hougen	53	Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D.	53	Senior Vice President, Drug Discovery and Corporate Development
Patrick R. O'Neil, Esq.	41	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

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 served as our Corporate Secretary through 2014 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.

SARAH BOYCE

Chief Business Officer

Ms. Boyce joined Isis in January 2015 as our Chief Business Officer. Prior to joining Isis, Ms. Boyce was Vice President, Head of International Business Strategy and Operations at Forest Laboratories, Inc. from 2012 to 2014. She was Vice President, Global Head Nephrology Therapeutics Area of Alexion Pharmaceuticals from 2010 to 2011. She held various positions at Novartis Group AG, including Vice President, Global Program Head, Pediatric and Specialty from 2000 to 2010. Prior to that, Ms. Boyce held positions at Bayer Pharmaceuticals and Roche.

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. Starting in January 2015, Mr. O'Neil also serves as our Corporate Secretary. 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 and our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 are approved for marketing, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 our or our partners' drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

In particular, even though KYNAMRO is approved for HoFH in the United States, it may not be commercially successful.

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, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, unaffordable.

If we fail to compete effectively, our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, will not contribute significant revenues.

Our competitors engage in 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, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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, which is approved, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 such products. 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 Pharmaceuticals, Inc. received approval from the FDA and the European Medicines Agency to market its MTP inhibitor, lomitapide, as an adjunct to a low-fat diet and other lipid-lowering treatments in patients with HoFH. Our revenues and financial position could suffer if KYNAMRO cannot compete effectively in the marketplace.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, drugs like tafamadis, diflunisal, and patisiran could compete with ISIS-TTR$_{Rx}$, drugs like Glybera, pradigastat and CAT-2003 could compete with ISIS-APOCIII$_{Rx}$, and RG7800 and olesoxime and the other products that may emerge from early development programs designed to treat patients with SMA could compete with ISIS-SMN$_{Rx}$.

KYNAMRO is, and, following approval any of our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, could be, subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including our approved drug, KYNAMRO, and our drugs in development including: ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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, when 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 or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 and the long term supply of KYNAMRO drug substance. 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 or initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved in additional markets 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, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, before they 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. It is possible that other regulatory agencies will not approve KYNAMRO or any of our other drugs including, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$ 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, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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. For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States or initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 and sales to patients, 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, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, do 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 and the Phase 3 studies for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. 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 the clinical studies, including any further studies under the development program for KYNAMRO and the Phase 3 studies for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 receipt of marketing approval for our drugs, including additional approvals for KYNAMRO, and initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. 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 and initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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, 2014, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $257.8 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. 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 AstraZeneca, Biogen Idec, Genzyme, GSK, and Roche 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 AstraZeneca, Biogen Idec, Genzyme, GSK, or Roche, 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, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 or milestones related to the Phase 3 programs for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, the price of our securities could decrease.

For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

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, and in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. These lawsuits 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.

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, 2014, we had cash, cash equivalents and short-term investments equal to $728.8 million. If we do not meet our goals to successfully commercialize KYNAMRO and our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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, 2014, the market price of our common stock ranged from $22.25 to $67.12 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, changes in payors' reimbursement policies, 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.

If a natural or man-made disaster strikes our research, development or manufacturing facilities or otherwise affects our business, 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. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government including the FDA.

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 11.2 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 in the past experienced periods 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. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or 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 17, 2015, 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 28,700 square foot manufacturing facility and a 25,800 square foot building adjacent to our manufacturing facility. Our 28,700 square foot facility houses manufacturing suites for our drug development business built to meet cGMP requirements and our 25,800 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 28,700 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 25,800 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. Akcea intends to lease space in Cambridge, Massachusetts; their primary place of business. We believe our existing facilities are adequate for our requirements in the foreseeable future and that we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs, including for the Phase 3 clinical trials for ISIS-TTR_{Rx}, ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$.

Item 3. Legal Proceedings

Santaris Litigation

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). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion.

In March 2014, Santaris filed a motion asking the court to decide that Santaris' alleged infringing sales of our patented methods are not actionable as a matter of law. In June 2014, the court granted Santaris' motion and dismissed our allegations to the extent the allegations are based on Santaris' sale or offer for sale of such method claims; and that we did not plead sufficient facts to establish that Santaris entering into its agreement with Enzon constituted the sale or offer for sale of the compounds claimed in U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739. The rest of the case is proceeding, and on October 17, 2014, we filed an amended complaint to plead additional facts and assert Santaris infringed U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739 through Santaris' agreement with Enzon.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Isis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents will infringe those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

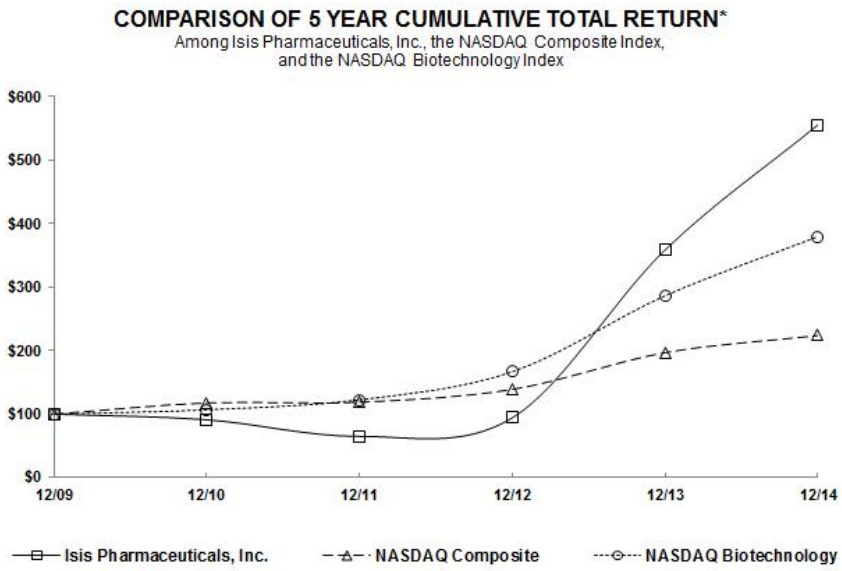
Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by The Nasdaq Global Select Market. These prices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

	HIGH	LOW
2014		
First Quarter	$ 62.66	$ 38.04
Second Quarter	$ 45.04	$ 22.25
Third Quarter	$ 43.42	$ 27.37
Fourth Quarter	$ 67.12	$ 35.26
2013		
First Quarter	$ 19.53	$ 10.36
Second Quarter	$ 28.66	$ 15.92
Third Quarter	$ 39.83	$ 23.63
Fourth Quarter	$ 42.69	$ 29.41

As of February 23, 2015, there were approximately 642 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, 2009 in our common stock, the NASDAQ Composite Index (total return) and the NASDAQ Biotechnology Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



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

	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14
Isis Pharmaceuticals, Inc.	$ 100.00	$ 91.09	$ 64.90	$ 93.97	$ 358.60	$ 555.72
NASDAQ Composite Index	$ 100.00	$ 117.61	$ 118.70	$ 139.00	$ 196.83	$ 223.74
NASDAQ Biotechnology Index	$ 100.00	$ 106.73	$ 122.40	$ 166.72	$ 286.55	$ 379.71

(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 Financial Data

Set forth below are our selected consolidated financial data (in thousands, except per share amounts):

	Years Ended December 31,				
	2014	2013	2012	2011	2010
Consolidated Statement of Operations Data:					
Revenue	$ 214,161	$ 147,285	$ 102,049	$ 99,086	$ 108,473
Research, development and patent expenses	$ 241,751	$ 184,033	$ 158,458	$ 157,397	$ 145,160
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (38,984)	$ (60,644)	$ (65,478)	$ (84,801)	$ (61,251)
Basic and diluted net loss per share attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.33)	$ (0.55)	$ (0.65)	$ (0.85)	$ (0.62)
Shares used in computing basic and diluted net loss per share	117,691	110,502	100,576	99,656	99,143

	As of December 31,				
	2014	2013	2012	2011	2010
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 728,832	$ 656,761	$ 374,446	$ 343,664	$ 472,353
Working capital	$ 721,265	$ 637,698	$ 349,116	$ 284,027	$ 377,247
Investment in Regulus Therapeutics Inc.(1)	$ 81,881	$ 52,096	$ 33,622	$ 4,424	$ 870
Total assets	$ 955,809	$ 847,156	$ 545,686	$ 484,894	$ 550,477
Long-term debt and other obligations, less current portion	$ 582,697	$ 370,954	$ 288,598	$ 232,924	$ 199,175
Accumulated deficit	$ (1,006,594)	$ (967,610)	$ (906,966)	$ (841,488)	$ (756,687)
Stockholders' equity	$ 257,780	$ 378,390	$ 182,766	$ 171,434	$ 244,542

(1) In October 2012, Regulus completed an IPO and we changed to accounting for our investment in Regulus at fair value from the equity method because our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. For additional information, see Note 2, *Investment in Regulus Therapeutics Inc.*in the Notes to the Consolidated Financial Statements.

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

Overview

We are the leading company in RNA-targeted drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class 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 with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs. Our business strategy is supported by our platform technology, our robust pipeline of drugs and our diverse partnering strategies, which have enabled us to focus on doing what we do best – to discover and develop novel antisense drugs.

Our novel lipid-lowering 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. Genzyme, a Sanofi Company, has also obtained marketing approval in other countries, including Mexico, Argentina, South Korea and Peru, and is pursuing marketing approval in multiple additional markets. Genzyme is evaluating KYNAMRO in a late-stage clinical study, FOCUS FH, in patients with severe HeFH, and they plan to report data from this study in 2015.

The efficiency and broad utility of our drug discovery technology supports the continued growth of our pipeline of antisense drugs. To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. Most recently, we established a wholly owned subsidiary, Akcea to develop and commercialize the drugs from our lipid franchise. Akcea will focus on the development and commercialization of ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$ as well as more potent follow on drugs for these programs. To lead Akcea, we hired a senior business leader with commercialization expertise in severe and rare and cardiovascular diseases to maximize the value of our lipid franchise assets. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

Another component of our partnering strategy is to form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as when we licensed KYNAMRO to Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK, Janssen and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Additionally, with Janssen we have a global collaboration to discover and develop antisense drugs to treat autoimmune disorders of the GI tract, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs to treat autoimmune disorders in the GI tract. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of companies that can exploit our drugs and technology. We call these companies satellite companies. 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. For example, Regulus is a satellite company partner that we co-founded to discover and develop antisense drugs targeting microRNAs. We sold a portion of our Regulus stock in 2014 for more than $20 million of cash, and we remain a significant shareholder in the company. We also maintain our broad RNA technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnering strategy, which we designed to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated seven new partnerships that involve antisense drugs for the treatment of various disorders, including neurological diseases, autoimmune disorders of the GI tract and cancer. We formed a broad alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders in the GI tract, four strategic alliances with Biogen Idec to discover and develop antisense drugs to treat neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. Additionally, we and our partner, GSK, are developing five drugs, including ISIS-TTR$_{Rx}$, which is in Phase 3 development. We have the potential to earn significant revenue from these partnerships and our other partnered programs. Since 2007 we have received more than $1.4 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn over $9 billion in future milestone payments and licensing fees from all of our partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements.

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. Through December 2014, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Business Segments

Prior to 2015, we operated in a single segment, Drug Discovery and Development Operations, because our chief decision maker reviewed operating results on an aggregate basis and managed our operations as a single operating segment. 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 or best-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 in which 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, with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer.

In 2015, we began operating as two segments. Our Drug Discovery and Development Operations segment and our new segment, Akcea, which is our newly formed wholly owned subsidiary. We formed Akcea to develop and commercialize the drugs from our lipid franchise, focusing on the clinical development of ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$, as well as more potent follow on drugs from these programs.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States. 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 and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

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 appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance; and
- Determining the fair value of convertible debt without the conversion feature.

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 the 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 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 stand-alone 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 global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the collaboration, we received a $25 million upfront payment in December 2012 and a $6 million payment in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. We also granted AstraZeneca options to license up to three cancer drugs under the separate research program. We were responsible for completing IND-enabling studies for ISIS-AR-2.5$_{Rx}$, which we completed in early 2014. We are also responsible for completing an ongoing clinical study of ISIS-STAT3-2.5$_{Rx}$, which we plan to complete in the first quarter of 2015. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. 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 when we entered into the agreement 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-STAT3-2.5$_{Rx}$ for the treatment of cancer;
- The development services we are performing for ISIS-STAT3-2.5$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AR-2.5$_{Rx}$ and the research services we performed for ISIS-AR-2.5$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we are performing for this program.

We determined that the ISIS-STAT3-2.5$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3-2.5$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3-2.5$_{Rx}$ 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 considered the ISIS-STAT3-2.5$_{Rx}$ license and the development services for ISIS-STAT3-2.5Rx to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3-2.5$_{Rx}$ license immediately because we delivered the license and earned the revenue. We are recognizing as revenue the amount allocated to the development services for ISIS-STAT3-2.5$_{Rx}$ over the period of time we perform services, which we expect will end during the first quarter of 2015. The ISIS-AR-2.5$_{Rx}$ license is also an exclusive license. At the inception of the agreement, ISIS-AR-2.5$_{Rx}$ was in an early stage of research. Therefore, we concluded that our knowledge and expertise with antisense technology was essential for AstraZeneca or another third party to successfully develop ISIS-AR-2.5$_{Rx}$. As a result, we determined that the ISIS-AR-2.5$_{Rx}$ license did not have stand-alone value and we combined the ISIS-AR-2.5$_{Rx}$ license and related research services into one unit of accounting. We recognized revenue for the combined unit of accounting over the period of time we performed services, which ended in the first quarter of 2014. 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 are recognizing revenue for the combined unit of accounting over the period of our performance.

We determined that the initial 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. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. 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 allocable consideration 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-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$ 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 $25 million upfront payment for the ISIS-STAT3-2.5$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3-2.5$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed 10 percent increase or decrease in the estimated selling price of the ISIS-STAT3-2.5$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3-2.5$_{Rx}$ license would change by approximately seven percent, or $0.8 million, 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 outlining 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. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations may change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize in future periods.

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. For example, since early 2012 we have entered into four collaboration agreements with Biogen Idec:

- 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 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 a Phase 2 clinical trial.

- 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.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen Idec to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen Idec exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug identified during the six year term of this collaboration, while Biogen Idec is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen Idec the option 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 research and/or 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 all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements 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 four 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 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 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 we or our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered 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 us or 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 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 immediately. 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 access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen Idec substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we considered milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provided Alnylam ongoing access to our technology to develop and commercialize RNAi therapeutics. 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 in 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 do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. We consider most milestone payments 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. 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. For example, during 2014, we recognized $9.5 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Valuation of Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months 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 income (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 our investments in equity securities in publicly-held biotechnology companies; 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 us to develop our own assumptions. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. We determine 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 ended. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

In November 2014, we participated as a selling shareholder in Regulus' equity offering and as a result we were subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, our equity securities of Regulus included a lack of marketability discount, and as a result, were classified as a Level 3 investment. At December 31, 2013, we did not have any investments classified as Level 3.

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 price of these publicly-held companies as a separate component of comprehensive income (loss). We account for our equity investment in the privately-held company under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. The cost method investment we hold is in one of our satellite companies and realization of our equity position in the company is uncertain. In circumstances where realization of our investment is uncertain, 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 2014, we realized a net gain on investments we sold of $21.2 million, consisting primarily of the $19.9 million gain we realized when we sold a portion of our stock in Regulus. 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. During 2013, we realized a $2.4 million net gain on investments related to the sale of stock in several of our satellite companies. During 2012, we realized a net gain on investments of $19.8 million primarily because of the increase in Regulus' valuation resulting from its IPO.

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 $1.3 million, $6.4 million and $0.8 million for the years ended December 31, 2014, 2013 and 2012, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values. In 2013, we conducted a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. As a result, our write-downs in 2013 were more significant than other years. We expect write-downs in future years to be similar to amounts recorded in 2012 and 2014.

Estimated Liability for Clinical Development Costs

We record accrued liabilities related to expenses for which service providers have not yet billed us. These liabilities are for 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 numerous 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 clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. 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 our convertible debt instruments, including our 1 percent and 2¾ percent convertible notes, 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 a similar debt instrument does not exist, we estimate the 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.

We assign a value to the debt component of our convertible 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 the convertible 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.

Results of Operations

Years Ended December 31, 2014 and December 31, 2013

Revenue

Total revenue for the year ended December 31, 2014 was $214.2 million compared to $147.3 million for 2013. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees. For example, nearly two-thirds of our revenue in 2014 was from milestone payments we earned due to the success of our drugs and partnerships.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2014 was $202.5 million compared to $144.2 million for 2013. 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, nearly two-thirds of our revenue in 2014 was from milestone payments we earned from the success of our drugs and partnerships. We earned $135.0 million in milestone payments during 2014 compared to $82.8 million in 2013. The revenue from milestone payments in 2014 was primarily comprised of:

- $80 million from Biogen Idec, for advancing ISIS-SMN$_{Rx}$, including initiating two Phase 3 studies, initiating a Phase 1 study of ISIS-DMPK-2.5$_{Rx}$, validating two undisclosed targets to treat neurological disorders under our neurology collaborations, and advancing a third drug into development;
- $28.5 million from GSK related to advancing the Phase 2/3 study of ISIS-TTR$_{Rx}$, and further advancing ISIS-HBV$_{Rx}$, ISIS-GSK4-L$_{Rx}$, and ISIS-RHO-2.5$_{Rx}$;
- $22.1 million from AstraZeneca related to the initiation of a Phase 1 clinical study of ISIS-AR-2.5$_{Rx}$ and advancing ISIS-STAT3-2.5$_{Rx}$; and
- $4 million from Achaogen when Achaogen initiated a Phase 3 study of plazomicin.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2014 was $11.6 million and increased compared to $3.1 million for 2013. The increase in 2014 was primarily a result of the $9.5 million in revenue we earned from Alnylam related to its license of our technology to one of its partners.

Operating Expenses

Operating expenses for the year ended December 31, 2014 were $261.9 million compared to $199.0 million for 2013. The expected increase in operating expenses was primarily due to higher costs associated with our Phase 3 programs for ISIS-TTR$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-APOCIII$_{Rx}$ and an increase in stock compensation expense due to the increase in our stock price. As drugs move forward to more advanced stages of development, including into longer and larger clinical studies, the costs of development increase. In addition to the Phase 3 programs we are conducting, we initiated Phase 2 studies for several drugs in our pipeline in the second half of 2013, which are ongoing in 2014, and advanced numerous drugs into clinical development in 2014.

In order to analyze and compare our results of operations to other similar companies, we believe 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. Non-cash compensation expense related to equity awards increased significantly in 2014 compared to 2013 primarily due to the increase in our stock price.

Research, Development and Patent Expenses

Our research, development and patent 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, development and patent expenses (in thousands):

	Year Ended December 31,	
	2014	2013
Research, development and patent expenses	$ 215,908	$ 174,360
Non-cash compensation expense related to equity awards	25,843	9,673
Total research, development and patent expenses	$ 241,751	$ 184,033

For the year ended December 31, 2014, total research, development and patent expenses were $215.9 million compared to $174.4 million for 2013, and were higher primarily due to more costs incurred in 2014 compared to 2013 associated with the clinical studies of the three drugs we currently have in Phase 3 studies, which we continued to advance. In addition, we progressed numerous drugs in our pipeline into later stage clinical trials. We initiated Phase 2 studies for several of the drugs in our pipeline beginning in the second half of 2013, which were ongoing in 2014, and we have advanced several drugs into clinical development. 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 partners. Antisense drug discovery is also the function that is responsible for advancing our 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,	
	2014	2013
Antisense drug discovery expenses	$ 43,620	$ 42,402
Non-cash compensation expense related to equity awards	7,290	2,878
Total antisense drug discovery	$ 50,910	$ 45,280

Antisense drug discovery costs were $43.6 million for the year ended December 31, 2014, and were essentially flat compared to $42.4 million for 2013. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Year Ended December 31,	
	2014	2013
KYNAMRO	$ 5,359	$ 7,653
ISIS-TTR_{Rx}	10,927	4,174
ISIS-SMN_{Rx}	19,064	6,938
ISIS-$APOCIII_{Rx}$	9,337	5,730
Other antisense development products	44,913	29,129
Development overhead costs	31,318	24,171
Total antisense drug development, excluding non-cash compensation expense related to equity awards	120,918	77,795
Non-cash compensation expense related to equity awards	9,640	3,202
Total antisense drug development	$ 130,558	$ 80,997

Antisense drug development expenditures were $120.9 million for the year ended December 31, 2014 compared to $77.8 million for 2013. Expenses in 2014 were higher compared to 2013 primarily due to the progression of numerous drugs in our pipeline into later stage clinical trials, including our three drugs currently in Phase 3 trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies the costs of development increase. Beginning in the second half of 2013, we initiated Phase 2 studies for several of the drugs in our pipeline, which are ongoing, and we advanced several drugs into clinical development. In addition, we incurred more costs in 2014 compared to 2013 associated with the clinical studies of ISIS-TTR_{Rx}, ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$, as we continued to advance those drugs. We began separately disclosing ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$ in the table above in 2014 because we initiated Phase 3 trials for these drugs during the year. All amounts exclude non-cash compensation expense related to equity awards. In 2014, we began presenting salaries and benefits in the development overhead costs line in our antisense drug development table. We have adjusted 2013 to conform to the current year presentation.

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 may 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 drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, 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 costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. We and Genzyme share development costs equally until 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,	
	2014	2013
Manufacturing and operations	$ 24,763	$ 20,509
Non-cash compensation expense related to equity awards	2,934	1,295
Total manufacturing and operations	$ 27,697	$ 21,804

Manufacturing and operations expenses for the year ended December 31, 2014 were $24.8 million, and increased compared to $20.5 million for 2013, primarily because we manufactured more drug product to support the increase in our drug development activities. In 2014, our manufacturing expenses included drug product to support the Phase 3 trial for ISIS-APOCIII$_{Rx}$ and additional costs associated with manufacturing drug product using our LICA technology. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

In our research, development and patent 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,	
	2014	2013
Personnel costs	$ 9,875	$ 9,571
Occupancy	7,357	6,897
Patent expenses	2,933	10,321
Depreciation and amortization	2,243	2,464
Insurance	1,197	1,108
Other	3,002	3,293
Total R&D support costs, excluding non-cash compensation expense related to equity awards	26,607	33,654
Non-cash compensation expense related to equity awards	5,979	2,298
Total R&D support costs	$ 32,586	$ 35,952

R&D support costs for the year ended December 31, 2014 were $26.6 million compared to $33.7 million for 2013 and decreased primarily due to lower patent expenses in 2014. Patent expenses were higher in 2013 primarily due to non-cash charges for patents and patent applications that we wrote off in 2013 due to a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. 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,	
	2014	2013
General and administrative expenses	$ 14,600	$ 13,173
Non-cash compensation expense related to equity awards	5,540	1,745
Total general and administrative	$ 20,140	$ 14,918

General and administrative expenses for the year ended December 31, 2014 were $14.6 million and increased compared to $13.2 million for 2013. The increase was due to consulting expenses we incurred. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the year ended December 31, 2014 totaled $2.7 million compared to $2.1 million for 2013. The increase in investment income was primarily due to a higher average cash balance and increased yields.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent convertible notes, non-cash interest expense related to the long-term financing liability for our primary facility and other miscellaneous debt.

The following table sets forth information on interest expense (in thousands):

	Year Ended December 31,	
	2014	2013
2¾ % convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 7,211	$ 6,758
Interest expense payable in cash	5,074	5,534
1 % convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	2,365	—
Interest expense payable in cash	597	—
Non-cash interest expense for long-term financing liability	6,622	6,568
Other	340	495
Total interest expense	$ 22,209	$ 19,355

Interest expense for the year ended December 31, 2014 was $22.2 million compared to $19.4 million in 2013. The increase in interest expense was primarily due to a higher average carrying value of the liability portion of our debt and a slight increase in interest expense payable in cash because we had more debt outstanding in 2014 compared to 2013. In November 2014, we completed a $500 million convertible debt offering. The notes mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes to repurchase $140 million in principal of our 2¾ percent notes. The new principal balance of the 2¾ percent notes is $61.2 million. We record non-cash amortization of the debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature. This means we recorded our convertible notes at a discount that we are amortizing over the life of the notes as non-cash interest expense.

Gain on Investments, Net

Net gain on investments for the year ended December 31, 2014 was $1.3 million compared to $2.4 million for 2013. The net gain on investments in 2014 was primarily due to the $1.3 million gain we realized when we sold the common stock of Achaogen we owned. During 2013, the gain consisted of sales of stock we held in several satellite companies.

Gain on Investment in Regulus Therapeutics Inc.

In 2014, we realized a gain on our investment in Regulus of $19.9 million when we sold a portion of our stock. We did not sell any of our stock in Regulus in 2013.

Early Retirement of Debt

In 2014, we recorded a $8.3 million non-cash loss on early retirement of debt, reflecting the early retirement of a large portion of our 2¾ percent convertible notes in November 2014. We did not recognize any loss on early retirement of debt in 2013.

Income Tax Benefit

In 2014, we recorded a net tax benefit of $15.4 million, of which $12.8 million related to our application of the intraperiod tax allocation rules that required us 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 gains on our equity investment in Regulus. In addition, $4.3 million of the tax benefit we recorded in 2014 related to a tax refund we expect to receive in the first quarter of 2015 from the State of California Franchise Tax Board related to the California franchise taxes we paid for the tax year ended December 31, 2009. Our income tax benefit in 2013 was $5.9 million. The increase in 2014 compared to 2013 was due to larger unrealized gains year over year and the tax refund we recorded in 2014.

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2014 was $39.0 million compared to $60.6 million for 2013. Basic and diluted net loss per share for the year ended December 31, 2014 was $0.33 per share compared to $0.55 per share for 2013. Our net loss for the year ended December 31, 2014 decreased significantly compared to 2013 due to the significant increase in revenue that we earned from our partners in 2014, offset mostly by the planned increase in operating expenses associated with our advancing pipeline of drugs. The decrease in our net loss was further impacted by the $19.9 million gain we realized in 2014 from the sale of a portion of our stock in Regulus, the $15.4 million net tax benefit we recorded in 2014 offset, in part, by the $8.3 million non-cash loss we recorded in 2014 on the early retirement of a large portion of our 2¾ percent convertible notes.

Net Operating Loss Carryforward

At December 31, 2014, we had federal and California tax net operating loss carryforwards of approximately $671.9 million and $888.7 million, respectively. Our federal tax loss carryforwards begin to expire in 2023. Our California tax loss carryforwards began to expire in 2014. At December 31, 2014, we also had federal and California research and development tax credit carryforwards of approximately $86.0 million and $34.5 million, respectively. Our Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless we use them prior to expiration. Our California research and development tax credit carryforwards are available indefinitely. Our net operating loss and research and development 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 research and development tax credit carryforwards.

Years Ended December 31, 2013 and December 31, 2012

Revenue

Total revenue for the year ended December 31, 2013 was $147.3 million compared to $102.0 million for 2012. 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. In 2013, we earned $82.8 million in revenue from milestone and licensing payments including:

- $26.5 million from GSK because we advanced ISIS-TTR$_{Rx}$, ISIS-HBV$_{Rx}$, formerly ISIS-GSK3$_{Rx}$, and ISIS-GSK4-L$_{Rx}$ in development;
- $25 million from Genzyme when the FDA approved the KYNAMRO NDA;
- $10 million when AstraZeneca added a second development candidate, ISIS-AR-2.5$_{Rx}$, to our collaboration;
- $17 million from Biogen Idec because we advanced the Phase 2 study of ISIS-SMN$_{Rx}$ in infants and for selecting and advancing ISIS-DMPK-2.5$_{Rx}$ in development; and
- $3.5 million when Xenon licensed XEN701.

Our revenue in 2013 also included $64 million primarily from the amortization of upfront fees and manufacturing services performed for our partners.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2013 was $144.2 million compared to $96.4 million for 2012. The increase in 2013 was primarily due to an increase in revenue from milestone payments we received and amortization of upfront fees.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2013 was $3.1 million and decreased compared to $5.6 million for 2012. The decrease was primarily due to $0.8 million in sublicensing revenue that we earned from Alnylam in 2013 compared to $2.7 million we earned from Alnylam in 2012.

Operating Expenses

Operating expenses for the year ended December 31, 2013 were $199.0 million compared to $171.0 million for 2012. The increase in operating expenses was primarily due to higher costs associated with the advancement and expansion of our pipeline.

Research, Development and Patent Expenses

Our research, development and patent 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, development and patent expenses (in thousands):

	Year Ended December 31,	
	2013	2012
Research, development and patent expenses	$ 174,360	$ 151,212
Non-cash compensation expense related to equity awards	9,673	7,246
Total research, development and patent expenses	$ 184,033	$ 158,458

For the year ended December 31, 2013, we incurred total research, development and patent expenses of $174.4 million compared to $151.2 million for 2012. Research, development and patent expenses in 2013 were higher primarily due to higher development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials, including advancing ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$. We also initiated numerous clinical studies and added new drugs to our pipeline. 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,	
	2013	2012
Antisense drug discovery expenses	$ 42,402	$ 34,035
Non-cash compensation expense related to equity awards	2,878	2,108
Total antisense drug discovery	$ 45,280	$ 36,143

Antisense drug discovery costs were $42.4 million for the year ended December 31, 2013 compared to $34.0 million for 2012. Expenses increased in 2013 compared to 2012 primarily due to an increase in activities to support our Biogen Idec and AstraZeneca research collaborations, a $1.5 million payment we made to CHDI, and additional supplies used in our research activities. Under the terms of our agreement with CHDI, we reimbursed CHDI for a portion of its support of our Huntington's disease program out of the $30 million upfront payment we received from our alliance with Roche to develop treatments for Huntington's disease. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Year Ended December 31,	
	2013	2012
KYNAMRO	$ 7,653	$ 9,451
ISIS-TTR$_{Rx}$	4,174	5,034
ISIS-SMN$_{Rx}$	6,938	3,903
ISIS-APOCIII$_{Rx}$	5,730	3,104
Other antisense development products	29,129	27,959
Development overhead costs	24,171	21,110
Total antisense drug development, excluding non-cash compensation expense related to equity awards	77,795	70,561
Non-cash compensation expense related to equity awards	3,202	2,482
Total antisense drug development	$ 80,997	$ 73,043

Antisense drug development expenditures were $77.8 million for the year ended December 31, 2013 compared to $70.6 million for 2012. The higher expenses in 2013 were primarily due to an increase in development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials, including advancing ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$. The increase associated with these activities was offset, in part, by lower development expenses related to KYNAMRO and ISIS-TTR$_{Rx}$. We initiated a Phase 2/3 clinical study of ISIS-TTR$_{Rx}$ in February 2013, for which we incurred a significant portion of the start-up expenses in 2012. All amounts exclude non-cash compensation expense related to equity awards. In 2014, we began presenting salaries and benefits in the development overhead costs line in our antisense drug development table. We have adjusted 2013 and 2012 to conform to the current year presentation.

Manufacturing and Operations

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

	Year Ended December 31,	
	2013	2012
Manufacturing and operations	$ 20,509	$ 19,232
Non-cash compensation expense related to equity awards	1,295	999
Total manufacturing and operations	$ 21,804	$ 20,231

Manufacturing and operations expenses for the year ended December 31, 2013 were $20.5 million, and increased slightly compared to $19.2 million for 2012, primarily because we manufactured more drug product due to our advancing and expanding pipeline. 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,	
	2013	2012
Personnel costs	$ 9,571	$ 9,231
Occupancy	6,897	6,909
Patent expenses	10,321	3,868
Depreciation and amortization	2,464	3,129
Insurance	1,108	1,143
Other	3,293	3,104
Total R&D support costs, excluding non-cash compensation expense related to equity awards	33,654	27,384
Non-cash compensation expense related to equity awards	2,298	1,657
Total R&D support costs	$ 35,952	$ 29,041

R&D support costs for the year ended December 31, 2013 were $33.7 million compared to $27.4 million for 2012. Expenses increased in 2013 compared to the same period in 2012 primarily due to non-cash charges for patents and patent applications that we wrote off in 2013 due to a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. 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,	
	2013	2012
General and administrative expenses	$ 13,173	$ 11,190
Non-cash compensation expense related to equity awards	1,745	1,325
Total general and administrative	$ 14,918	$ 12,515

General and administrative expenses for the year ended December 31, 2013 were $13.2 million and increased compared to $11.2 million for 2012 primarily due to higher personnel expenses. All amounts exclude non-cash compensation expense related to equity awards.

Equity in Net Loss of Regulus Therapeutics Inc.

We recognized $1.4 million for equity in net loss of Regulus for the year ended December 31, 2012. We used the equity method of accounting to account for our investment in Regulus until Regulus' IPO in October 2012. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. Therefore, we did not recognize any equity in net loss of Regulus in 2013.

Investment Income

Investment income for the year ended December 31, 2013 totaled $2.1 million compared to $1.8 million for 2012. The increase in investment income was primarily due to a higher average cash balance and increases in yields.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs on our convertible notes, non-cash interest expense related to the long-term financing liability for our primary facility, and interest expense payable in cash for our convertible notes and other miscellaneous debt related items.

The following table sets forth information on interest expense (in thousands):

	Year Ended December 31,	
	2013	2012
Convertible Notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 6,758	$ 9,846
Interest expense payable in cash	5,534	4,306
Non-cash interest expense for long-term financing liability	6,568	6,502
Other	495	498
Total interest expense	$ 19,355	$ 21,152

Interest expense for the year ended December 31, 2013 was $19.4 million compared to $21.2 million in 2012. The decrease in interest expense was primarily due to a decrease in amortization of the debt discount related to our 2¾ percent notes. The borrowing rate for our 2¾ percent notes was less than the rate for our 2⅝ percent notes because of market conditions at the time of each issuance. As a result, we amortized less debt discount for the 2¾ percent notes compared to the 2⅝ percent notes. This decrease was partially offset by an increase in interest expense payable in cash because the interest rate was slightly higher on our 2¾ percent notes compared to our 2⅝ percent notes.

Gain on Investments, Net

Net gain on investments for the year ended December 31, 2013 was $2.4 million compared to $1.5 million for 2012. The net gain on investments in 2013 was primarily due to the $1.1 million gain we realized when we sold the stock we held in Sarepta Therapeutics, Inc., and the $0.8 million payment we received from Pfizer, Inc. related to its acquisition of Excaliard Pharmaceuticals, Inc. During 2012 we recognized a $1.5 million net gain on investments, which consisted primarily of the $1.3 million payment we received from Pfizer, Inc. related to its acquisition of Excaliard.

Gain on Investment in Regulus Therapeutics Inc.

Our gain on Regulus in 2012 was $18.4 million and was in the fourth quarter of 2012 because of the increase in Regulus' valuation resulting from its IPO. We did not sell any of our holdings of Regulus in 2013.

Early Retirement of Debt

Loss on early retirement of debt for the year ended December 31, 2012 was $4.8 million, reflecting the early redemption of our 2⅝ percent convertible notes in the second half of 2012. We did not recognize any loss on early retirement of debt in 2013.

Income Tax Benefit

In 2013, we recorded a tax benefit of $5.9 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 unrealized gains on our equity investments in our satellite companies, including Regulus. Our income tax benefit declined from $9.1 million in 2012 because the unrealized gains in 2013 were not as large as in 2012.

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2013 was $60.6 million compared to $65.5 million for 2012. Basic and diluted net loss per share for the year ended December 31, 2013 was $0.55 per share compared to $0.65 per share for 2012. Our net loss in 2013 decreased compared to 2012 due to a decrease in our net operating loss resulting primarily from the significant increase in revenue that we earned from our partners in 2013. The decrease in our net operating loss was partially offset by the following items that occurred in 2012 and did not reoccur in 2013:

- $18.4 million gain we realized in 2012 because of the increase in Regulus' valuation resulting from its IPO; and
- $4.8 million loss, $3.6 million of which was non-cash, we recorded in 2012 on the early retirement of our 2⅝ percent convertible subordinated notes.

Net Operating Loss Carryforward

At December 31, 2013, we had federal and California tax net operating loss carryforwards of approximately $685.8 million and $894.9 million, respectively. We also had federal and California research credit carryforwards of approximately $62.6 million and $22.2 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, 2014, we have earned approximately $1.5 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, 2014, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $1.3 billion under long-term debt arrangements to finance a portion of our operations.

At December 31, 2014, we had cash, cash equivalents and short-term investments of $728.8 million and stockholders' equity of $257.8 million. In comparison, we had cash, cash equivalents and short-term investments of $656.8 million and stockholders' equity of $378.4 million at December 31, 2013. We received a substantial amount of cash in 2014, including more than $230 million in payments from our partners, which demonstrates our robust partnership strategy and advancing pipeline. Additionally, we received cash from the issuance of our 1 percent convertible notes and stock option exercises.

At December 31, 2014, we had consolidated working capital of $721.3 million compared to $637.7 million at December 31, 2013. Working capital increased significantly in 2014 primarily due to the cash we received in 2014 from our partners and the increase in the carrying value of our investment in Regulus.

As of December 31, 2014, our debt and other obligations totaled $643.5 million compared to $283.5 million at December 31, 2013. The increase was primarily due to the 1 percent senior convertible notes we issued in November 2014, somewhat offset by the repurchase of $140 million principal amount of our 2¾ percent notes. 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, 2014. 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions) Total	Less than 1 year	1-3 years	3-5 years	After 5 years
1 percent convertible senior notes (principal and interest payable)	$ 535.0	$ 5.0	$ 10.0	$ 10.0	$ 510.0
2¾ percent convertible senior notes (principal and interest payable)	$ 69.5	$ 1.5	$ 3.4	$ 64.6	$ —
Facility rent payments	$ 131.8	$ 6.2	$ 13.1	$ 13.9	$ 98.6
Equipment financing arrangements (principal and interest payable)	$ 3.3	$ 2.8	$ 0.5	$ —	$ —
Other obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Capital lease	$ 0.2	$ 0.2	$ —	$ —	$ —
Operating leases	$ 25.1	$ 1.6	$ 3.0	$ 3.0	$ 17.5
Total	$ 766.2	$ 17.4	$ 30.1	$ 91.6	$ 627.1

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

Convertible Debt Summary

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the new principal balance of the 2¾ percent notes is $61.2 million.

At December 31, 2014 our outstanding convertible debt was as follows (amounts in millions unless otherwise noted):

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Outstanding principal balance	$ 500.0	$ 61.2
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually for both the 1 percent and 2¾ percent notes. The convertible notes are convertible under certain conditions, at the option of the note holders. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both.

1 Percent Convertible Senior Notes

We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 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 1 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.

2¾ Percent Convertible Senior Notes

We may 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.

Equipment Financing Arrangement

In October 2008, we entered into an equipment financing loan agreement, 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 and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.39 percent. As of December 31, 2014, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.18 percent. The carrying balance under this loan agreement at December 31, 2014 and 2013 was $3.2 million and $7.5 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Research and Development 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 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 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, 2014 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, reputable financial institutions, corporations, U.S. government agencies and securities issued by states of the United States and political subdivisions of the states 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 2014 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

We maintain 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) that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2014.

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, 2014, we assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting under the 2013 "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission, under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on that assessment, our management concluded that we maintained effective internal control over financial reporting as of December 31, 2014.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2014, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

The above assessment 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, 2014, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (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, 2014, 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, 2014 and 2013, 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, 2014 of Isis Pharmaceuticals, Inc. and our report dated February 27, 2015 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 27, 2015

Item 9B. Other Information

Not applicable.

Item 10. Directors, Executive Officers and Corporate Governance

Biographies of the Directors Whose Terms Expire at the 2015 Annual Meeting of Stockholders. These Directors will be Nominees for Election for a Three-Year Term at the 2015 Annual Meeting.

Frederick T. Muto, age 61, has served as a Director of Isis since March 2001. Mr. Muto joined the law firm of Cooley LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is Chair of the firm's Business Department and a founding partner of Cooley LLP's San Diego office.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because, with 35 years of experience at one of the country's leading law firms focused on life sciences and technology companies, he provides us important advice regarding our strategic transactions, corporate governance and compensation matters.

Breaux B. Castleman, age 74, has served as a Director of Isis since June 2013. Since August 2001, Mr. Castleman has been president and chief executive officer of Syntiro Healthcare Services, Inc., a health care investment company, which recently sold its operations as a service provider of integrated care management and disease management. Mr. Castleman has been a director of USMD Holdings, Inc., a physician-led integrated healthcare system, since September 2009 and was a director of MELA Sciences, Inc., a medical device company, from 2003 until 2011.

The Board believes that Mr. Castleman is uniquely suited to serve on the Board and the Audit Committee because he has significant experience in strategic planning and financial engineering for Fortune 1000 companies and has financial advisory expertise in the life sciences industry.

Biographies of the Directors Whose Terms Expire at the 2016 Annual Meeting of Stockholders.

Stanley T. Crooke, M.D., Ph.D., age 69, 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 worked for SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

The Board believes Dr. Crooke is uniquely suited to serve on the Board primarily because as the Chief Executive Officer and founder of Isis he has dedicated over 25 years to the discovery and development of antisense, our technology platform. He is the named inventor on some of the key patents in the field of RNA-targeted therapeutics, and has over 30 years of drug discovery and development experience.

Joseph Klein, III, age 53, has served as a Director of Isis since December 2005. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy, for Medical Manager Corporation, a leading developer of physician office management information systems. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund, Inc. Mr. Klein serves on the board of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds. Mr. Klein also serves on the boards of private and non-profit entities. Within the last five years, Mr. Klein formerly served on the board of directors of five publicly held biotechnology companies: BioMarin Pharmaceutical Inc., NPS Pharmaceuticals, Inc., OSI Pharmaceuticals, Inc., PDL BioPharma, Inc. and Savient Pharmaceuticals, Inc.

The Board believes that Mr. Klein is uniquely suited to serve on the Board and the Audit Committee because he is a Chartered Financial Analyst, and because he has extensive public company, venture investment, board, and financial advisory expertise in the life sciences industry.

Joseph Loscalzo, age 63, is Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School, Chairman of the Department of Medicine, and Physician-in-Chief at Brigham and Women's Hospital. Dr. Loscalzo received his A.B. degree, summa cum laude, his Ph.D. in biochemistry, and his M.D. from the University of Pennsylvania. His clinical training was completed at Brigham and Women's Hospital and Harvard Medical School, where he served as Resident and Chief Resident in medicine and Fellow in cardiovascular medicine. Post-training, Dr. Loscalzo joined the Harvard faculty and staff at Brigham and Women's Hospital in 1984. He rose to the rank of Associate Professor of Medicine, Chief of Cardiology at the West Roxbury Veterans Administration Medical Center, and Director of the Center for Research in Thrombolysis at Brigham and Women's Hospital. He joined the faculty of Boston University in 1994, first as Chief of Cardiology and, in 1997, Wade Professor and Chair of Medicine, Professor of Biochemistry, and Director of the Whitaker Cardiovascular Institute. He returned to Harvard and Brigham and Women's Hospital in 2005.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board primarily because of his extensive scientific expertise, including 25 years of research in the areas of vascular biology, thrombosis, and atherosclerosis, and practical knowledge as a practicing physician. Dr. Loscalzo's expertise and role as a leading cardiologist is particularly valuable as we mature and grow our cardiovascular franchise.

Biographies of the Directors Whose Terms Expire at the 2017 Annual Meeting of Stockholders.

Spencer R. Berthelsen, M.D., age 62, has served as a Director of Isis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 370 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He has been Chairman of their Board of Directors since October 2001. He has served as a Clinical Professor of Medicine at Baylor College of Medicine and the University of Texas Health Science Center of Houston. Dr. Berthelsen served on the board of the Texas Academy of Internal Medicine in the past and the Caremark National Pharmacy and Therapeutics Committee from 1999 through 2005.

The Board believes Dr. Berthelsen is uniquely suited to serve on the Board because of his current position managing a large multi-specialty group practice and 32 years of experience as a practicing physician.

B. Lynne Parshall, age 60, 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 through December 31, 2012. She also served as our Corporate Secretary through 2014, and has served with the Company 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. Ms. Parshall serves on the board of directors of Regulus Therapeutics, Inc. and Cytokinetcs Inc., two biopharmaceutical companies. Within the last five years, Ms. Parshall formerly served as a Director of CardioDynamics International Corporation and Corautus Genetics Inc., both biopharmaceutical companies.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the Chief Operating Officer and an executive of the Company for over 20 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 25 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 70, has served as a Director of Isis since January 1994. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He is also an Independent Trustee of the Schwab Family of Funds and Director of Grandpoint Capital, a bank holding company. Mr. Wender also is a managing partner and owns, with his wife, Colgin Cellars. As of March 2014, Mr. Wender is a director of Outfront Media, lessors of advertising space on out-of-home advertising structures.

The Board believes Mr. Wender is uniquely suited to serve on the Board primarily because, with over 40 years of experience as an investment banker with Goldman, Sachs & Co., he provides Isis important advice regarding our financial reporting, corporate finance matters, strategic transactions, and compensation matters. Mr. Wender is also highly qualified to serve on the Audit Committee.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our Directors, executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock and other equity securities. Officers, Directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2014, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

Code of Ethics and Business Conduct

We have adopted a Code of Ethics that applies to all officers, Directors and employees. We have posted our Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at www.isispharm.com.[1]

Identification of Audit Committee and Financial Expert

We have a separately designated Audit Committee. The members of the Audit Committee are Mr. Castleman, Mr. Klein, and Mr. Wender. Our Audit Committee charter requires that each member must be independent and the Board has determined that each of the members of the Audit Committee are independent within the meaning of the applicable The Nasdaq Global Select Market listing standards and SEC rules and regulations.

In addition, all Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by SEC regulations. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 40 years of experience as an investment banker with Goldman, Sachs & Co.

[1] Any information that is included on or linked to our website is not part of this Form 10-K.

Item 11. Executive Compensation

Compensation Discussion and Analysis

Overview

Since inception, the Isis mission has been to create a new, more efficient technology for drug discovery and development, antisense technology, and exploit that technology to create a pipeline of first-in-class medicines to treat a wide range of diseases. Today, thanks to the innovation and perseverance of Isis, we believe antisense technology is taking its place as the third platform for drug discovery alongside small molecules and protein therapeutics.

Through the efficiency of our technology platform and business strategy we have built a pipeline of 38 drugs in development with under 400 employees, representing a ratio of 1 drug: 12 employees.

Isis is focused on innovation. Isis has implemented a unique business strategy that is intended to support long-term innovation based on the efficiency of antisense technology. Isis has created a unique innovation-focused, science–driven, culture that couples with the technology and business model to ensure long-term productivity and a commitment to the patients we serve.

Antisense technology exists today primarily because of the innovation at Isis. We have more than 1,300 issued patents that provide substantial control of key elements of the technology for many years to come. This intellectual property has been critical in the completion of partnerships that have resulted in over $1.4 billion in cash since 2007 and the development of a consortium of companies who advance the technology alongside us, and thereby increase our reach. We should continue to realize the value of our partnerships, and our consortium of companies, for many years to come in the form of license fees, milestone payments and royalties. Isis has been recognized as one of the top ten most innovative companies in the Biotechnology industry, based on number of granted patents, scientific strength, industry impact, technology strength and research intensity. Our nearly 1,900 issued patents and applications are all the more remarkable given that Isis has fewer than 400 employees. This means Isis has produced nearly five issued patents and applications per employee.

A key component of our business and organizational strategy is to maintain an optimal size to foster innovation. We believe the optimal size is approximately 400 employees. To maintain this optimal size we license our medicines at key value inflection points during development, thus avoiding the need to build the large, complex, inefficient organizations associated with fully integrated pharmaceutical companies. We also demand more of every employee at Isis and do not tolerate mediocrity. We have been remarkably successful in achieving these goals. Today we have 38 new medicines in development; one medicine in development per 12 employees. And we believe this productivity is sustainable. We plan to add three to five new medicines to the pipeline every year without significant increases in the number of employees.

By design, Isis demands more of every employee, particularly the middle and senior level leaders. This requires us to design our compensation system to recruit, motivate and retain outstanding individuals. Here too, we have been successful. Our average employee turnover rate over the last five years (reflected as of 3rd quarter each year) has averaged 7% per year, while the average turnover in the San Diego/La Jolla area for biotech/pharmaceutical companies over this period was 12.8% according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

In summary, at Isis, our vision is clear and designed to promote long-term creation of value through innovation, and bring benefit to generations of patients with many diseases. Our vision is to:

- create and constantly advance a new, more efficient drug discovery platform, antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- demand more of every employee - more commitment, more knowledge, more intensity, more innovation and more productivity;
- aggressively manage average and below average performance so every employee produces more; and
- demand great performance and pay for that performance.

Summary of Compensation Practices

Below we summarize some of our compensation practices, both the practices we implement because we believe they are consistent with our vision and building long-term stockholder value (see "What We Do" below), and those we choose not to implement as we believe they are counter to our vision and building long-term stockholder value (see "What We Don't Do" below):

What We Do	What We Don't Do
Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity	**Do not guarantee a cash bonus – cash bonuses can, and have been, zero**
Reward productivity and performance	**Do not provide perquisites for any employees**
Recognize the value of long-term employees and low turnover	**Do not provide "gross-up" payments, other than for relocation**
Use a balanced mix of fixed and variable cash incentives and long-term equity incentives	**Do not allow pledging, shorting or hedging against our stock**
Evaluate compensation compared to the 50th percentile of our peer group	**Do not reprice or "cash-out" stock options without stockholder approval**
Design our compensation philosophy and objectives to mitigate unnecessary or imprudent business risk taking	
Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year	
Place a m aximum limit on Performance MBOs	
Set a strict budget for equity awards and salary increases	
Set the size of equity awards based on individual and company performance	
Require minimum vesting periods for equity awards	
Maintain equity holding periods that require our named executive officers and non-employee Board members to hold shares received from their RSUs until they meet certain ownership thresholds or no longer serve the company	
Maintain equity holding periods that require our employees to hold ESPP shares for a minimum of six months	
Require our executive officers and VPs to trade Isis' stock through Rule 10b5-1 trading plans	
Use a "double trigger" for cash payments for change of control	
Use an executive "claw-back" policy	
Use an independent compensation consultant engaged by the Compensation Committee	

Compensation Overview and the Role of the Compensation Committee

We have designed our executive compensation program to attract and retain executives who can help us meet our business objectives and to motivate our executives to enhance long-term stockholder value. The Compensation Committee of the Board of Directors, with input from an independent compensation consultant, manages and oversees our executive compensation program. At the end of each year, and as otherwise required, the Compensation Committee approves the total compensation for each of our executive officers. In addition, the full Board of Directors reviews and approves the Compensation Committee's recommendations regarding the compensation of executive officers.

The Compensation Committee's responsibilities include:

- reviewing and approving overall compensation strategy;
- reviewing and approving corporate performance goals and objectives relevant to the compensation of our executive officers;
- evaluating and recommending to the Board the compensation plans and programs advisable for Isis, as well as modifying or terminating existing plans and programs;
- establishing policies with respect to stock compensation arrangements;
- reviewing and approving compensation arrangements for our executive officers, including our Chief Executive Officer;
- reviewing and approving compensation arrangements for our Directors;
- administering our stock-based awards and ESPP;
- evaluating risks associated with our compensation policies and practices and assessing whether these risks are reasonably likely to have a material adverse effect on us;
- selecting and retaining a qualified, independent compensation consultant;
- performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- reporting to the Board of Directors from time to time, or whenever it is called upon to do so.

As the SEC continues to adopt the final rules implementing and defining the Dodd-Frank legislation, Isis' management and the Compensation Committee will:

- monitor the SEC's adoption of the final rules and definitions; and
- adjust Isis' compensation policies as necessary to satisfy the new rules.

Independent Compensation Consultant

The Compensation Committee has the authority and budget to hire an independent compensation consultant as it deems necessary. The Compensation Committee has retained Barney & Barney LLC as its independent compensation consultant. Barney & Barney LLC primarily provided the Compensation Committee advice in the following areas:

- selecting the 2014 Executive Peer Group;
- evaluating the pay mix for our named executive officers; and
- evaluating short-term and long-term incentives for our executive officers.

Barney & Barney LLC did not provide any additional services to us or our affiliates.

Compensation Philosophy

Our compensation philosophy supports and rewards the characteristics and behaviors we believe will make us successful:

Pay for Performance. We incorporate a number of features into our compensation structure to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking. We use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives. Our Performance MBOs are not guaranteed (i.e. are 100% at risk) and include a multiplier, or performance factor, based on Isis' and the employee's performance. Therefore, if *either* Isis or the employee does not perform well, the Performance MBO can be, and has been, zero.

CEO Pay Ratio. An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest levels of compensation received by an employee. Dr. Crooke's total cash compensation, over the last three years, was on average 24.3 times that of the average cash compensation for our lowest level employees and 1.92 times greater than the average of our other executive officers. We cover the specific elements of our compensation structure in more detail below.

Business Objectives

As noted above, our vision is clear and is designed to promote long-term creation of value through innovation, and bring benefit to generations of patients with many diseases. Our vision is to:

- create and constantly advance a new, more efficient drug discovery platform, antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- demand more of every employee - more commitment, more knowledge, more intensity, more innovation, more productivity;
- aggressively manage average and below average performance so that every employee produces more; and
- demand great performance and pay for that performance.

Drug discovery and development across a portfolio of many drugs (currently 38 for Isis) is a long process that spans many years, where decisions we make today can have a positive or negative consequence five years, ten years, and even further into the future. As such, it is essential we set goals that incentivize our employees to execute our long-term strategy, because we believe our long-term strategy should continue to reward our stockholders into the future.

Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees.

For us to retain our technology leadership and effectively manage the technical complexity and broad scope of our development pipeline, our most senior executives must advance multiple drug strategies and collaborative partnerships in parallel and consistently over many years, versus emphasizing one or two at the expense of others that deserve attention. As a result, other than stock price, we do not use financial-based metrics as objectives, such as earnings per share, because financial metrics typically overly emphasize two or three annual business metrics and ignore the complexity of the tasks we are undertaking. By taking this approach, we avoid the temptation to deviate from creating fundamental long-term value to meet a short-term metric.

We structure our corporate objectives so they are results driven rather than task driven. We typically include a number of objectives that are based on achieving positive data in the clinic. For example, in 2014 we had a corporate objective to advance our pipeline with one of the measures being to achieve positive data from three Phase 2 studies. This type of objective only rewards our executives if the data are positive - we do this to encourage the prudent spending of stockholder money on development decisions. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of "bad bets."

At the beginning of each year, we set aggressive corporate objectives that our Board approves. On at least a quarterly basis, the Board evaluates our progress in achieving these objectives. We define excellent performance as a year in which we have met most of our objectives.

Importance of Tenure; Our Investment in Knowledge-Rich Employees

It takes a significant period of time and a substantial investment to recruit and develop executives who possess the experience and talent necessary to lead at Isis given our innovative technology, innovative business strategy and complex drug development pipeline. Senior executives must have experience with all aspects of our business to be effective leaders. Our drug technology is a "platform technology", which means the more knowledge and experience an employee has with our technology platform, the better equipped she or he is to create value at Isis. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is critical to our future success. For these reasons, it is our objective to attract and retain the best talent available and to invest in those individuals who deliver long-term productivity.

- Long tenure among a dedicated and highly skilled workforce, combined with the highest performance standards, contributes to our leadership in the industry and serves the interests of stockholders.
- Our focus on retention is coupled to a strong belief that executive talent most often should be developed and promoted from within Isis.
- The long tenure of high-performing executive officers reflects this strategy at all levels of the organization.
  - Our named executive officers, or NEOs, who served in 2014 have tenures at Isis ranging from 14 years to 26 years.
  - Our other officers who served in 2014 have on average 12 years of tenure at Isis.
- Each of the executive officers has been carefully evaluated and selected through a rigorous performance assessment process over a long career. In their current assignments, they remain subject to a challenging annual performance assessment in which they must continue to meet the highest standards or be reassigned or separated from the Company.

Elements of Executive Compensation

Employees in our organization do not share either accountability or responsibility equally for strategic and/or tactical decisions. It is well ingrained in our culture that not everyone should share the same level of risk/reward for the consequences of these decisions. As a result, we have structured the various components of our compensation system to reflect accountability both for the successes and failures (both long-term and short-term) of Isis and our employees. We pay our senior management team for results and their use of judgment in executing the strategies they have established. Therefore, the more senior a person becomes within Isis, the more the person's cash compensation will be "at risk." We compensate the more junior employees for accomplishing their work well and, therefore, a lower portion of their cash compensation is "at risk."

The more senior role a person plays, the more that person's cash compensation will be "at risk."

Our executive officers' total direct compensation consists of four elements:

(1) base salary,

(2) MBO – Performance Based – At Risk Cash Compensation, no portion of which is guaranteed,

(3) stock-based compensation, and

(4) the same benefits, including 401(k) matching, that we provide to all employees.

The MBO – Performance Based – At Risk Cash Compensation is the only element that does not apply to all employees. Individual Performance MBOs are available only to employees at the director level and above.

We consider many factors in determining the amounts we grant to our executives for each of the above three compensation elements. These factors include:

- company-wide performance, including achievement of corporate objectives;
- the Compensation Committee's assessment of our CEO's and executive officers' individual performance;
- competitive compensation practices;
- increased efficiencies and process improvements;
- effective collaboration and teamwork;
- individual expertise, skills and knowledge;
- the need to retain and motivate;
- the impact an individual's judgment has on our success or failure; and
- the advice of the Compensation Committee's independent compensation consultant.

The Compensation Committee relies on these and other factors such as general economic conditions, industry conditions, and the Compensation Committee's collective business judgment in setting and/or approving the appropriate increases. We do not have specific weightings assigned to these factors, as the importance of each factor can vary among the executive officers and from year to year.

Peer Group

The Compensation Committee considers relevant market pay practices when setting executive compensation to ensure our ability to recruit and retain high performing talent.

As part of setting the 2014 compensation, the Compensation Committee, in consultation with its independent compensation consultant, evaluated and selected a peer group of 25 life science companies for evaluating Isis' compensation (the "Executive Peer Group"). The Compensation Committee reviews the compensation of our NEOs against the Executive Peer Group's executive compensation to ensure that our compensation is competitive and to inform and shape its decision-making when setting compensation. However, the Compensation Committee does not strictly adhere to quantitative benchmarks.

The Executive Peer Group, which the Compensation Committee reviews on an annual basis, consists of companies that generally:

- are similar to Isis in terms of certain factors, including one or more of the following: size (i.e., revenue, market capitalization), industry, and stage of development;
- have named executive officer positions that are comparable to ours in terms of breadth, complexity and scope of responsibilities; and
- compete with us for executive talent.

The Executive Peer Group does not include companies headquartered outside the United States (because compensation and benefit practices are generally different outside the United States, the comparable compensation data for the named executive officers is not available and cost of living is different) or companies in industries whose compensation programs are not comparable to our programs, such as non-life science companies.

In June of 2014, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publically available data as of April 2014. The Compensation Committee noted Isis' market capitalization was approximately $4.9 billion and had increased approximately 30% since the Compensation Committee last set the Executive Peer Group. As part of this process, the Compensation Committee looked at companies in Isis' industry with market capitalizations of between $1 billion and $8 billion, including looking at companies that identified Isis as a peer, so called "reverse peers". Based on this evaluation, the Compensation Committee added Akorn, NPS Pharmaceuticals, Pacira Pharmaceuticals and Pharmacyclics to the Executive Peer Group, as these companies fell within the market capitalization range, were in Isis' sector, and some were reverse peers. Additionally, the Compensation Committee removed Array BioPharma and Infinity Pharmaceuticals because they were below the market capitalization range, and removed ViroPharma because it was acquired by Shire. As of December 31, 2014, Isis' market capitalization had increased significantly to approximately $7.3 billion.

The following table lists the companies in the 2014 Executive Peer Group, along with Isis' rankings among these companies, based on market capitalization, and financial data reported by each company for the most recently-reported fiscal year at the time the Compensation Committee selected the Executive Peer Group, in June 2014.

Company (ticker)	Annual Revenues (in millions)	Market Capitalization (in millions)	Stage of Lead Drug
Accorda Therapeutics (ACOR)	$ 336.4	$ 1,589.2	Market
Akorn (AKRX)	$ 317.7	$ 2,094.5	Market
Alkermes (ALKS)	$ 575.6	$ 6,400.5	Market
Alnylam Pharmaceuticals (ALNY)	$ 47.2	$ 4,194.2	Phase III
Arena Pharmaceuticals (ARNA)	$ 81.4	$ 1,462.5	Market
Ariad Pharmaceuticals (ARIA)	$ 45.6	$ 1,501.8	Market
Auxilium Pharmaceuticals (AUXL)	$ 400.7	$ 1,406.3	Market
Exelixis (EXEL)	$ 31.3	$ 718.1	Market
Halozyme Therapeutics (HALO)	$ 54.8	$ 1,505.4	Market
ImmunoGen (IMGN)	$ 35.5	$ 1,255.1	Market
Incyte Corporation (INCY)	$ 354.9	$ 9,015.1	Market
InterMune (ITMN)	$ 70.3	$ 3,307.2	Phase III
Jazz Pharmaceuticals (JAZZ)	$ 872.4	$ 8,137.7	Market
Lexicon Pharmaceuticals (LXRX)	$ 2.2	$ 930.0	Phase III
MannKind (MNKD)	$ 0.0	$ 2,636.7	Phase III
Medivation (MDVN)	$ 272.9	$ 4,980.0	Market
Momenta Pharmaceuticals (MNTA)	$ 35.5	$ 606.1	Market
Nektar Therapeutics (NKTR)	$ 148.9	$ 1,590.7	Market
NPS Pharmaceuticals (NPSP)	$ 155.6	$ 3,104.1	Market
Pacira (PCRX)	$ 85.6	$ 2,326.9	Market
Pharmacyclics (PCYC)	$ 260.2	$ 7,644.9	Market
Seattle Genetics (SGEN)	$ 269.3	$ 5,400.2	Market
The Medicines Company (MDCO)	$ 687.9	$ 1,620.8	Market
Theravance (THRX)	$ 4.8	$ 3,437.7	Market
United Therapeutics (UTHR)	$ 1,117.0	$ 4,874.6	Market
Isis Pharmaceuticals, Inc. (ISIS)	$ 147.3	$ 4,958.2	Market
Isis' Ranking	14	7	NA
Isis' Percentile Rank	46%	75%	NA

The table below compares total cash compensation and the total direct compensation of our NEO's against that of the 50th percentile of the Executive Peer Group.

	2014 Total Cash Compensation (in thousands)		2014 Total Direct Compensation (in thousands)	
Name	NEO	50th Percentile of Executive Peer Group	NEO	50th Percentile of Executive Peer Group
Stanley T. Crooke	$ 1,488,488	$ 1,327,900	$ 6,228,143	$ 4,126,200
Elizabeth L. Hougen	$ 584,600	$ 585,100	$ 1,741,542	$ 1,425,900
B. Lynne Parshall	$ 1,130,924	$ 855,100	$ 3,232,043	$ 2,864,500
Richard Geary	$ 636,066	$ 372,300	$ 1,785,888	$ 575,200
Brett Monia	$ 630,139	*	$ 1,787,115	*

*Due to the unique and complex nature of Dr. Monia's position at Isis, the outside compensation consultant advised the Compensation Committee that there were no appropriate comparable positions within the Executive Peer Group.

Total cash compensation in 2014 for our CEO, Dr. Crooke, was within +/- 20% of the 50th percentile of the Executive Peer Group. Dr. Crooke's total direct compensation was above the 50th percentile of the Executive Peer Group due to the exceptional increase in Isis' stock price.

Our Productivity vs. Executive Peer Group

All companies in all industries strive to be more productive than their peers. Leadership management and compensation systems are all focused on enhancing long term productivity. However, measurement of productivity is challenging, particularly in biotechnology.

Even for established R&D based pharmaceutical companies for which the comparator group is obvious, comparisons of productivity are challenging. While revenues and profits per employee may be good measures for a portion of the equation, they are inadequate because they provide little insight into potential for topline sales growth and no insight into innovation, which is the foundation for long-term sustainable growth. To provide insight into these attributes, measures of the size, maturity and potential value of the drug pipeline are necessary. Additionally, measures of innovation such as numbers of issued patents can be used.

Because biotechnology companies' business models vary, ranging from companies repurposing a single in-licensed commercial drug, to companies developing in-licensed novel drugs, to true research-based companies and a few companies pioneering broad new technology platforms, comparisons of productivity within the biotechnology industry are even more challenging. Such comparisons are even more difficult for development stage pre-commercial companies.

Nevertheless, it is as important to develop productivity metrics and compare productivity for biotechnology companies as it is for any other industry. As Isis matures and achieves revenues from the commercial sale of its products, we will use revenue and profit per employee as metrics, supplemented by metrics that measure the value of our drug pipeline and innovation. We analyze our productivity against the Executive Peer Group and other leaders in drug development using, among other measures, number of drugs in clinical development per employee and number of patents per employee. The table below measures Isis on these productivity metrics against the median for the Executive Peer Group, and the leading company in the peer group for each productivity metric (based on the most recent Annual Report of the companies at the time the Compensation Committee selected the Executive Peer Group in June 2014):

	Drugs in Clinical Development per Employee	Patents per Employee
Isis' Ranking	1st	2nd
Executive Peer Group Median	1 drug for every 41 employees	1.22 patents per employee
Peer Leader for Drugs in Clinical Development per Employee (ImmunoGen)	1 drug for every 19 employees	NA
Peer Leader for Patents per Employee (Alnylam)	NA	4 patents per employee
Isis Pharmaceuticals, Inc. (ISIS)	1 drug for every 12 employees	3 patents per employee

As illustrated, Isis' innovative culture and business strategy have made Isis incredibly productive in terms of the number of drugs in development per employee and patents per employee.

Compensation Allocation/Pay Mix

A key element of our compensation philosophy is to monitor and adjust our pay mix for our senior management team so the pay mix is weighted less heavily on fixed compensation (salary) and more heavily weighted on at-risk cash compensation and long-term equity incentive compensation. As part of the Compensation Committee's review of our total pay mix for executive officers, the Compensation Committee implemented the following:

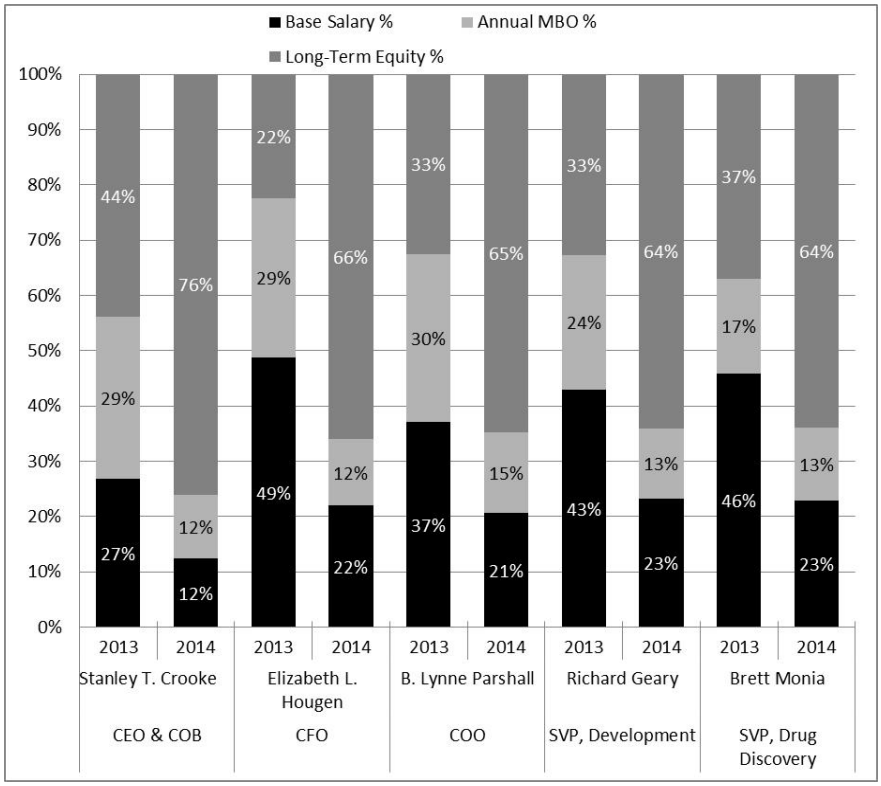
- *Salaries were frozen for most NEOs from 2011-2013.* The Compensation Committee did not increase salaries for the CEO and most of our NEOs for each of 2011, 2012 and 2013 to allow an increasing percentage of total compensation to be at risk;

- *A significant portion of cash compensation is at risk.* The Compensation Committee structures cash compensation such that a significant proportion of our CEO's, COO's and other NEO's cash compensation is at risk; and

- *More of total compensation is long-term equity.* The Compensation Committee adjusted the total pay mix for our CEO and other NEOs such that more of their compensation is in the form of long-term equity compensation.

An annual review of our total pay mix helps Isis compete for and retain talent in the competitive marketplace and maintain compensation equity and balance among positions with similar responsibilities. The target pay mix for our NEOs is a result of the compensation targets which emphasize long-term compensation versus short-term compensation. Actual salary levels, annual Performance MBO awards and long-term incentive awards will vary based on an individual's responsibilities, tenure in a particular position, experience, individual performance and company performance.

The following chart illustrates the portions of actual total direct compensation for the named executive officers that are composed of base salary, annual Performance MBO and long-term equity ($ shown in thousands) for 2013 and 2014:



Name	Year	Base Salary	Annual Performance MBO	Long-Term Equity	Base Salary %	Annual Performance MBO %	Long-Term Equity %
Stanley T. Crooke	2013	$ 735,169	$ 803,907	$ 1,203,708	27%	29%	44%
CEO & COB	2014	$ 768,252	$ 720,236	$ 4,720,669	12%	12%	76%
Elizabeth L. Hougen	2013	$ 365,496	$ 215,871	$ 167,880	49%	29%	22%
CFO	2014	$ 377,923	$ 206,677	$ 1,132,961	22%	12%	66%
B. Lynne Parshall	2013	$ 641,574	$ 526,171	$ 562,945	37%	30%	33%
COO	2014	$ 664,029	$ 466,895	$ 2,077,096	21%	15%	65%
Richard Geary	2013	$ 398,444	$ 225,918	$ 562,945	34%	19%	47%
SVP, Development	2014	$ 411,194	$ 224,872	$ 1,132,961	23%	13%	64%
Brett Monia	2013	$ 381,288	$ 142,983	$ 307,226	46%	17%	37%
SVP, Drug Discovery	2014	$ 396,158	$ 233,981	$ 1,132,961	23%	13%	64%

Base Salary

The fixed component of our compensation structure is base salary. We categorize our jobs in a system called broad-banding. That is to say there are relatively few job levels within Isis, specifically ten levels, but the scope of responsibility and accountability an employee may assume is broad. We do not have salary ranges, and therefore we do not set salary minimums or maximums. It is therefore possible that someone may be in a lower job level, but his or her salary may reach levels which exceed those of someone in a higher job level. We have chosen not to have salary ranges because years of experience have shown that this approach often creates unnecessary bureaucracy and a loss of talented individuals. Our aim is to attract and retain the most highly qualified employees in an extremely competitive market.

We determine base compensation levels for all our employees primarily by market forces. Accordingly, the Compensation Committee believes that it is important when making its compensation decisions to be informed as to the current practices of comparable publicly held companies with which we compete for top talent. To this end, the Compensation Committee reviews market and peer company data, which includes competitive information relating to the mix and levels of compensation for executives in the life sciences industry. We obtain this information for the Executive Peer Group based on recent public filings with the SEC. In addition, we also review data from the Radford Global Life Sciences Survey, which is a summary of compensation data submitted by over 500 life sciences companies. The Committee uses these data to inform and shape its decision-making but does not strictly adhere to quantitative benchmarks. In addition, we assess whether the scope of job responsibilities and internal equity warrant a given base salary.

Base salaries for CEO and COO were *frozen* for 2011-2013.

Base salary is guaranteed to all employees as wages for hours worked. It represents consideration for the performance of job responsibilities. This portion of total cash compensation is not at risk and may increase as a result of how well an individual performs his or her job responsibilities.

Each year our employees are eligible to receive an appropriate merit salary increase. The Compensation Committee sets a Company-wide merit increase budget percentage based on Isis' performance and external factors such as the average merit budget of comparable companies. The actual merit increase award for each employee, including our executive officers, will vary depending upon the respective employee's contributions to Isis. For example, for 2014 performance the Company-wide merit increase budget was 3.5%, with a range of individual merit award increases of 0% to 7.0%. However, regardless of individual employee variances, we do not exceed the Company-wide approved merit budget.

The Compensation Committee evaluates each executive officer's performance to set his or her annual merit increase. As part of this process, the Compensation Committee reviews the written reports prepared by the CEO evaluating the performance of each individual executive officer. The Compensation Committee carefully considers these reports since our CEO is in the best position to evaluate our executive officers' day-to-day and overall performance. The Compensation Committee meets in executive session and evaluates the CEO's performance, primarily based upon the CEO's achievement of our company's objectives for the year. At the end of this process, the Compensation Committee determines the CEO's merit increase and approves or recommends changes to the merit increases for the remaining executive officers. Our CEO has no role in determining his own compensation.

The executive officers' new salaries for each year are calculated as follows:

- Current Base Salary (x) Merit Increase = Increase to Base Salary
- Current Base Salary (x) Increase to Base Salary = New Base Salary

Performance MBOs can be, and have in the past been, zero.

Performance MBOs have a maximum limit.

For example, Dr. Crooke's 2015 salary of $800,518 was calculated as follows:

2014 Base Salary	(x)	Merit Increase	=	Increase to Base Salary
$768,252	(x)	4.2%	=	$32,266
Current Base Salary	(+)	Increase to Base Salary	=	New Base Salary in 2015
$768,252	(+)	$32,266	=	$800,518

When reviewing salaries, the Compensation Committee noted that our CEO's salary, and the salary of three of our other NEOs, was greater than the 50th percentile of the Executive Peer Group (two were below the 50th). The Compensation Committee also noted its desired target mix of compensation is less weighted on salary and historically did not increase base salaries for the CEO, COO and most of the other NEOs for 2011-2013 to help adjust total pay mix so that it was weighted less heavily on fixed cash compensation. Given Isis' outstanding 2014 performance, and given that most salaries were fixed for three years, the Compensation Committee approved merit increases to each of the NEO's salaries for 2015.

MBO-Performance Based-At Risk Cash Compensation (Performance MBO)

The next component of an executive officer's compensation, as well as the compensation of our employees at the director level and above, is a performance based cash payment through our Performance MBO program. Our Performance MBO program rewards employees for reaching specific objectives and for the judgment they use in making decisions, while an employee's base salary compensates the employee for his or her continued service and performance. We do not guarantee a Performance MBO as compensation. It is totally at risk. As such, a Performance MBO represents an opportunity for reward based upon the individual's level of accountability and depends on the relative success of both Isis and the individual. Our approach for awarding MBO bonuses differs from salary increases because, unlike salary increases, market forces do not impact bonus amounts.

We calculate the actual amount of each executive officer's respective Performance MBO based on the following formula:

Base Salary (x) Target MBO % (x) Company Performance Factor (x) Individual Performance Factor = Performance MBO Amount

Performance MBOs can be zero. The multipliers in this formula ensure we award bonuses based on *both* Isis' performance and individual performance. This means an employee may not receive a Performance MBO even if he or she performed well in a year in which the Company does not meet its corporate objectives. Similarly, if an employee performed poorly in a year in which the Company met its corporate objectives, he or she may not receive a Performance MBO.

For example, in 1999 no Performance MBOs for executive officers were paid due to the failures Isis faced at the time. In 2004 our CEO's Performance MBO was 64% of the Performance MBO he received in 2003 because of disappointing clinical trial results; the Company Performance Factor was 50% that year. Conversely, in 2007 Isis had a seminal year and we rewarded our executive officers consistent with Isis' success.

Performance MBOs have a maximum limit. Performance MBOs are limited by a maximum Company Performance Factor, maximum Individual Performance Factor and Target MBO Percentage:

- We have a maximum Company Performance Factor of 200% and a maximum Individual Performance Factor of 160%. This range represents the boundary conditions for our Performance Factors and ensures we reward our employees consistent with Isis' success.

- We base Target MBO Percentages on position levels within Isis. The Target MBO percentages for 2014 were: Directors 15%; Executive Directors 20%; Vice Presidents 25% or 30%; Senior Vice Presidents 35%, COO 45%; and CEO 60%.

An individual's Target MBO percentage does not change unless he or she changes position level or the Compensation Committee sets a new target for that level. The table below summarizes the minimum and maximum MBO for 2014 as a percentage of salary:

Name	Minimum MBO Percentage of Salary	Maximum MBO Percentage of Salary
Stanley T. Crooke	0%	192%
Elizabeth L. Hougen	0%	112%
B. Lynne Parshall	0%	144%
Richard Geary	0%	112%
Brett Monia	0%	112%

The Compensation Committee sets the Company Performance Factor based on the following process:

- Isis' achievement of the approved corporate objectives for the year. At the end of each year, the Compensation Committee meets to evaluate Isis' overall performance. As described below in the chart called "Evaluation of 2014 Corporate Objectives," the Compensation Committee measures Isis' performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management.

- In addition, the Compensation Committee considers our one-, three- and five-year total stockholder returns, and based on these returns may reduce the Individual Performance Factors for our executive officers.

- The Compensation Committee then reviews the Company Performance Factor history from the prior ten years to form a comparison for our current year's successes and/or failures.

- Finally, the Compensation Committee approves each executive officer's Individual Performance Factor based on the individual's performance.

Once the Compensation Committee has determined the elements of the formula above, we use that formula to calculate each executive officer's Performance MBO.

Evaluation of 2014 Corporate Objectives. On December 16, 2014, the Compensation Committee completed its evaluation of the Company's performance against the 2014 Corporate Objectives.

The Compensation Committee set the Company Performance Factor for the 2014 MBO at 125% due to our strong achievements for the year across drug discovery, development and corporate development, including the significant increase in the stock price, continued advancement of the ongoing Phase 3 study for ISIS-TTR_{Rx}, including an $18 million payment from GSK, advancing key programs into Phase 3 studies, and six positive efficacy studies for drugs in our pipeline. The table below provides a detailed evaluation of each objective and the related achievements:

Evaluation of 2014 Corporate Objectives		
	Objective & Pre-Approved Measures	**Evaluation**
1	Advance Pipeline: • Add four new drugs into pipeline • Initiate Phase 2 Clinical Trials on four drugs • Report positive Phase 2 clinical data on at least three drugs • Initiate Phase 3 Clinical Trials on ISIS-SMN_{Rx} (two patient populations) • Initiate Phase 3 Clinical Trials on ISIS-$APOCIII_{Rx}$ (two patient populations) • Continue to advance ongoing Phase 3 clinical trial for ISIS-TTR_{Rx} • Complete discussions with FDA and EMA that are supportive of advancing ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$ into Phase 3 clinical trials	Isis *exceeded* this objective: • Isis added six drugs to its pipeline • Isis and its partners initiated Phase 2 clinical studies for four drugs • Isis reported positive Phase 2 clinical data on seven drugs • Isis initiated ENDEAR and CHERISH, Phase 3 studies for ISIS-SMN_{Rx} • Isis initiated APPROACH, a Phase 3 study for ISIS-$APOCIII_{Rx}$ • Isis successfully advanced the ongoing Phase 3 Clinical Trial for ISIS-TTR_{Rx} • Discussions with FDA and EMA were supportive of advancing ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$ into Phase 3 clinical trials
2	Stock price increase by a percentage greater than or equal to median of the companies listed in the NASDAQ Biotechnology Index	Isis *exceeded* this objective: • Isis' stock price increased over 50% for the year while the median stock price change for companies listed in the NASDAQ Biotechnology Index increased 17%
3	Meet budget and financial projections for the year	Isis *exceeded* this objective: • Isis met its budget • Isis significantly exceeded its financial guidance for the year

	Objective & Pre-Approved Measures	Evaluation
4	Make Biogen Idec relationship successful: • Target sanction of at least two targets • Initiate Phase 1 clinical trial for ISIS-DMPK$_{Rx}$ • Identify at least two Collaboration Targets • Identify at least two Development Candidates • Achieve $120 million in revenue from relationship	Isis *exceeded* this objective: • Isis achieved target sanction for two targets under its Biogen Idec collaborations • Isis initiated a Phase 1/2 study of ISIS-DMPK-2.5$_{Rx}$ • Isis identified two collaboration targets under its Biogen Idec collaborations • Isis identified two Development Candidates under its Biogen Idec collaborations • Isis recognized over $123 million in revenue during 2014 under its Biogen Idec collaborations
5	Advance at least one LICA development candidate through IND-enabling toxicology studies	Isis *met* this objective: • Isis completed IND-enabling toxicology studies for a LICA development candidate
6	Strengthen clinical leadership and organization • Successfully integrate new medical leadership	Isis *exceeded* this objective: • Isis hired five new medical doctors into its clinical organization and successfully integrated them
7	Develop and execute long term commercialization/partnering strategy for ISIS-APOCIII$_{Rx}$	Isis *met* this objective: • Isis established Akcea Therapeutics to develop and commercialize the drugs from its lipid franchise
8	Complete an additional strategic partnership	Isis *met* this objective: • Isis formed an alliance with Janssen Biotech, Inc. to discover and develop antisense drugs to treat autoimmune disorders of the GI tract.
9	Achieve $18 million milestone for ISIS-TTR$_{Rx}$	Isis received an $18 million milestone payment from GSK related to advancing the Phase 2/3 study of ISIS-TTR$_{Rx}$
	Unplanned Accomplishments for 2014	
10	Isis successfully completed an offering of $500 million aggregate principal amount of Convertible Senior Notes due 2021 in a private placement. Isis used a significant amount of the net proceeds from the offering to repurchase a large portion of its 2 ¾% Convertible Senior Notes due 2019.	
11	Isis appointed Paula Soteropoulos as president and chief executive officer of Akcea Therapeutics.	
12	Isis strengthened its management team with the addition of Sarah Boyce as chief business officer.	
13	Isis published the Phase 2 clinical data of ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia in the New England Journal of Medicine.	
14	Isis published the Phase 2 clinical data of ISIS-FXI$_{Rx}$ in the New England Journal of Medicine.	
15	Isis formed an alliance with AstraZeneca to discover and develop novel delivery methods for antisense oligonucleotides.	
16	Isis generated cash from the sale of stock Isis owned in its satellite company partners of more than $25 million, including more than $20 million from the sale of Regulus stock.	
17	Isis favorably negotiated a tax benefit from the State of California Franchise Tax Board.	

Once the Committee establishes the Company Performance Factor, the Committee next reviews individual performance and sets each Executive Officer's Performance MBO payout. The following table illustrates the Performance MBOs approved for 2014 performance:

Name	Base Salary	Target MBO %	Company Performance Factor	Individual Performance Factor	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor[1]
Stanley T. Crooke[2]	$ 768,252	60%	125%	125%	$ 720,236	1-17
Elizabeth L. Hougen	$ 377,923	35%	125%	125%	$ 206,677	2,3,7,8,10 & 15-17
B. Lynne Parshall[2]	$ 664,029	45%	125%	125%	$ 466,895	1-17
Richard S Geary	$ 411,194	35%	125%	125%	$ 224,872	1-6, 9, 13 & 14
Brett Monia	$ 396,158	35%	125%	135%	$ 233,981	1-5, 8, 9 & 13-15

(1) The numbers correspond to the enumerated objectives in the table entitled "Evaluation of 2014 Corporate Objectives" on pages 119 through 120. The Compensation Committee reviews the individual's contribution towards the corporate objective when setting the Individual Performance Factor.

(2) Since our CEO and COO are ultimately responsible for the Company's performance, their Individual Performance Factors are usually the same as the Company Performance Factor.

The Company Performance Factor reflects a decrease of 10 percentage points from the 2013 Company Performance Factor of 135%, but reflects a very strong year of performance. As noted earlier, the corporate objectives are set and approved by our Board at the beginning of each year. We ensure these objectives are aggressive and we define excellent performance as a year in which we have met most of the objectives.

Stock Compensation

We use stock options and RSUs to give all employees, including Isis' executive officers, an economic interest in the long-term appreciation of our common stock. We believe awarding a combination of stock options and RSUs provides a number of benefits. Stock options provide a way to align employee interests with those of upper management and the stockholders because as our stock price increases, so too does the employee's compensation. In 2012, we started granting RSUs as part of the annual merit equity awards. RSUs are a strong retention vehicle for employees as the RSUs vest in annual installments over four years and have value upon vesting, but at the same time, require fewer shares than option awards.

Our Stock Awards reward performance and incentivize long-term stock appreciation and increased stockholder returns.

Some of our largest institutional stockholders agree our stock options are performance-based and the best vehicle for our long-term compensation. Our independent compensation consultant did not recommend we change our equity vehicles. Over the past several years we discussed our use of time-vested stock options and RSU awards with our institutional stockholders. The results of this process were that one of our largest institutional stockholders agreed that time-vested options are the best long-term incentive compensation vehicle for a biopharmaceutical company at our stage, and others agreed that our time-vested stock options are performance-based compensation. Our independent compensation consultant also believes time-vested stock options are performance-based compensation and an appropriate equity vehicle for Isis. Also we would be disadvantaged if we did not offer time-vested equity awards since most companies we compete with for talent (including most companies in the Executive Peer Group) do not use event-based vesting for equity compensation.

We grant existing employees new options and RSUs annually to provide a continuing financial incentive in Isis' long-term success. We set the size of the equity awards based on individual and company performance during the previous year.

Vesting schedules reward long-term performance and incentivize long-term stock appreciation and increased stockholder returns. For each stock option and RSU granted, the Compensation Committee sets a vesting schedule over four years, with no vesting during the first year. Therefore, the stock options and RSUs granted to our executive officers directly align the interests of our executive officers with the interests of our stockholders and Isis' long-term success. The actual economic value of stock option awards depends directly on the performance of our stock price over the period during which the awards vest and the period in which the options may be exercised. In other words, the stock options are not worth anything if our stock price does not increase above the exercise price. Our executive officers will only realize economic value when our stock price, and consequently stockholder value, increases. Similarly, in the same way our stockholder returns increase and decrease based on our stock's performance, the value to our employees of the RSUs increases and decreases based on our stock's performance.

We do not tie vesting to the achievement of specific events, such as annual metrics, because we do not want to encourage our employees to deviate from our company objectives, which we believe optimizes sustained stockholder value; nor do we want our employees to take unnecessary risks just to meet a short-term metric.

The stock option vesting schedule is typically over a 4-year period at the rate of 25% at the end of the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment. The RSU vesting schedule is typically over a 4-year period at the rate of 25% per year. In addition, as further described below, our executive officers must hold shares received upon vesting of their RSUs until they meet certain ownership thresholds or no longer serve the Company. These practices align our employee compensation with our stockholders' interests because if stockholder value declines over time, so too will the value of the equity compensation provided to all employees. We have historically had low employee turnover, particularly in our management team, and the members of our management have traditionally held their options for a long period of time before exercise. Our low turnover is indicative of our employees' commitment to Isis and its technology, and reflects our officers' belief in the long-term value of our stock.

Our stock compensation budget minimizes dilution. Each year the Compensation Committee approves a budget that sets the number of stock options and RSUs we can grant our employees for annual merit awards. We do not grant options or RSUs that exceed this budget without the Compensation Committee's approval. Over the past three years, the average merit award stock budget set by the Compensation Committee has been approximately 1.6% of our outstanding common stock on an issued and outstanding basis. This stock compensation budget, and therefore our equity compensation burn rate, is well below the Executive Peer Group average of 3.1% from 2011 through 2013. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2014 performance, the Compensation Committee set a merit stock award budget that resulted in 1.48 million stock options and 246,826 RSUs awarded to employees, including the executive officers. Together these shares represent approximately 1.5% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee's position level and performance in the previous year, ultimately determines the size of the individual annual stock grant.

Our executive officers and members of our Board of Directors must hold the shares issued under their RSUs until they have met an ownership guideline and all employees must hold shares purchased under our ESPP for six months.

In February 2013, our Compensation Committee and our Board approved stock ownership and holding guidelines for our executive officers and members of the Board. These guidelines require our executive officers and non-employee Board members to hold the shares they receive under their RSU awards until they achieve the guidelines or no longer serve the Company. Shares sold or surrendered to pay for withholding taxes associated with the RSU awards are exempt from these holding requirements.

The table below indicates the stock ownership guidelines for our executive officers and Board members:

Executive Officer/Director	Stock Ownership Guideline (as a multiple of base salary/annual cash retainer)
CEO[1]	3 times Base Salary
COO	2 times Base Salary
All other executive officers	1 times Base Salary
Non-employee Directors	4 times Annual Cash Retainer

(1) Dr. Crooke currently meets these ownership guidelines.

In addition, our ESPP has a six month minimum holding period for shares purchased under the ESPP.

Dr. Crooke currently holds approximately 725,000 shares of our common stock and has held these shares throughout his 25-year tenure. As of December 31, 2014, Dr. Crooke's holding represented approximately 55 times his Base Salary.

We have a recoupment/"clawback" policy. If we are required to prepare an accounting restatement due to the material noncompliance of Isis, as a result of misconduct, with any financial reporting requirement under the securities laws, Isis' Chief Executive Officer and Chief Financial Officer shall reimburse Isis for:

- any bonus or other incentive-based or equity-based compensation received by that person from Isis during the 12-month period following the first public issuance or filing with the SEC (whichever first occurs) of the financial document embodying such financial reporting requirement; and
- any profits realized from such executive's sale of Isis' securities during that 12-month period.

The SEC may exempt any person from the application of this executive recoupment policy, as it deems necessary and appropriate.

In addition, if and when the SEC adopts implementing regulations under Section 954, "Recovery of Erroneously Awarded Compensation" under The Dodd-Frank Wall Street Reform and Consumer Protection Act, our Nominating, Governance and Review Committee will promptly adopt appropriate updates to this policy to comport with such implementing regulations.

We explicitly prohibit employees from "shorting" and hedging against our stock and pledging our stock. To help avoid situations in which our employees may benefit from transactions that harm our stockholders, our policies specifically prohibit all employees, including our executive officers, from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price. In addition, we specifically prohibit all of our employees from pledging our stock and trading derivative instruments based on our common stock (e.g. put or call options for our stock).

10b5-1 plan required for executive officers and vice presidents. We have a Rule10b5-1 trading program. Our Rule 10b5-1 trading program allows our executive officers, vice presidents and other employees, to establish plans that permit prearranged future sales of his or her stock when there is no material non-public information available. We do not allow our executive officers or vice presidents to buy or sell our stock outside of the Rule 10b5-1 trading program except for purchases of our stock under our ESPP (but not subsequent sales of the stock) and transactions that are automatically effected by Isis' stock administrator in connection with the vesting and release of RSUs.

Perquisites

We are committed to using stockholder money responsibly, to building stockholder value and ensuring our processes are entirely transparent. As a result, Isis' policies do not provide for perquisites for any employees, including our executive officers.

Retirement & Other Benefits

We maintain a highly competitive position with regard to the benefits offered to all regular employees, including our executive officers. These benefits include medical, dental and vision insurance, EAP/WorkLife, basic life insurance, short-term disability/sick pay, long-term disability, vacation, holidays, a 401(k) plan with employer match, an ESPP and Accidental Death & Dismemberment (AD&D) insurance.

Recognizing that health care costs constitute a greater fraction of disposable income for lower paid employees, we have a progressive contribution premium for our health care benefits, which means the more money an Isis employee makes, the more he or she contributes to the costs of his or her family's health care.

Retention and Change of Control Agreements

We designed our retention agreements for our CEO and COO and the related severance compensation provisions to meet the following objectives:

Change in Control. As part of our normal course of business and as a result of our business strategy, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. Occasionally, a transaction in the biotech/biopharmaceutical industry may start as a licensing transaction, but ultimately result in an acquisition. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on pages 131 and 132, we provide a component of severance compensation for our CEO and COO to promote their ability to act in the best interests of our stockholders even though they could be terminated as a result of the transaction.

Termination without Cause. If we terminate the employment of our COO "without cause" we will pay her the benefits described under "Post-Employment Compensation – Retention and Change of Control Agreements." This agreement provides us with more flexibility to make a change in senior management if such a change is in our and our stockholders' best interests.

2014 Say-on-Pay Vote

We value the feedback our stockholders provide regarding executive compensation. As such, we are committed to providing our stockholders the opportunity for a "Say-on-Pay" vote annually.

In 2014 we asked our stockholders to provide a non-binding approval regarding our executive officer compensation for the previous year. This proposal, commonly known as a "Say-on-Pay" proposal, gave our stockholders the opportunity to express their views on the compensation paid to our NEOs. At our 2014 Annual Meeting of Stockholders, we received an advisory vote in favor of our executive compensation by over 98% of the shares voted at the meeting.

Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2014, 2013, and 2012, compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer and our three other most highly compensated executive officers at December 31, 2014, called our "named executive officers."

Summary Compensation Table

Name and Principal Position	Year	Salary ($)	Bonus[1] ($)	Stock Awards[2] ($)	Option Awards[2] ($)	All Other Compensation[3] ($)	Total ($)
Stanley T. Crooke	2014	$ 768,252	$ 720,236	$ 1,489,375	$ 3,231,294	$ 18,986	$ 6,228,143
Chairman, President, Chief	2013	$ 735,169	$ 803,907	$ 325,971	$ 877,737	$ 15,752	$ 2,758,536
Executive Officer	2012	$ 735,169	$ 367,585	$ 90,516	$ 344,921	$ 17,815	$ 1,556,006
Elizabeth L. Hougen	2014	$ 377,923	$ 206,677	$ 357,450	$ 775,511	$ 23,981	$ 1,741,542
Senior Vice President, Finance and	2013	$ 365,496	$ 215,871	$ [4] 54,419	$ [4] 113,461	$ 20,618	$ 769,865
Chief Financial Officer	2012	$ 337,036	$ 131,444	$ 16,462	$ 62,741	$ 21,148	$ 568,831
B. Lynne Parshall	2014	$ 664,029	$ 466,895	$ 655,325	$ 1,421,771	$ 24,023	$ 3,232,043
Director, Chief Operating Officer	2013	$ 641,574	$ 526,171	$ 152,482	$ 410,463	$ 20,636	$ 1,751,326
	2012	$ 641,574	$ 256,630	$ 52,136	$ 198,675	$ 22,600	$ 1,171,615
Richard S. Geary	2014	$ 411,194	$ 224,872	$ 357,450	$ 775,511	$ 16,861	$ 1,785,888
Senior Vice President, Development	2013	$ 398,444	$ 225,918	$ 82,117	$ 221,049	$ 14,695	$ 942,223
	2012	$ 398,444	$ 143,440	$ 23,583	$ 89,879	$ 17,048	$ 672,394
Brett Monia[5] Senior Vice President, Drug Discovery and	2014	$ 396,158	$ 233,981	$ 357,450	$ 775,511	$ 24,015	$ 1,787,115
Corporate Development	2013	$ 381,288	$ 142,983	$ 83,145	$ 224,081	$ 22,834	$ 854,331

(1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2015 we paid bonuses for 2014 performance.

(2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to our named executive officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5, *Stockholders' Equity*, regarding assumptions underlying valuation of equity awards.

(3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.

(4) Ms. Hougen received additional stock options and stock awards due to her promotion to Chief Financial Officer in January 2013.

(5) Mr. Monia was not a named executive officer in 2012 or 2013. We are not disclosing compensation for 2012 as permitted by SEC regulations.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2014, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2014

Name	Grant Date	All Other Stock Awards: Number of Shares of Stock or Units (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards ($/Sh)	Grant Date Fair Value of Stock and Option Awards[1] ($)
Stanley T. Crooke	1/2/14		187,500	$ 39.87	$ 3,231,294
	1/15/14	31,250			$ 1,489,375
Elizabeth L. Hougen	1/2/14		45,000	$ 39.87	$ 775,511
	1/15/14	7,500			$ 357,450
B. Lynne Parshall	1/2/14		82,500	$ 39.87	$ 1,421,771
	1/15/14	13,750			$ 655,325
Brett Monia	1/2/14		45,000	$ 39.87	$ 775,511
	1/15/14	7,500			$ 357,450
Richard S. Geary	1/2/14		45,000	$ 39.87	$ 775,511
	1/15/14	7,500			$ 357,450

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to our named executive Officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5, *Stockholders' Equity*, regarding assumptions underlying valuation of equity awards.

Narrative to Summary Compensation Table and Grants of Plan-Based Awards Table

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 2, 2014. All of these stock options were granted out of our 2011 Plan. The options have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

The Compensation Committee granted RSUs to the executive officers on January 15, 2014. All of these RSUs were granted out of our 2011 Plan. The RSUs vest at the rate of 25% per year over four years with a vesting commencement date of January 15, 2014.

Outstanding Equity Awards at Fiscal Year-End – Executive Officers.

The following table shows for the fiscal year ended December 31, 2014, certain information regarding outstanding equity awards at fiscal year-end for our named executive officers.

Other than the equity awards described in the table below, there were no equity incentive plan awards outstanding for our named executive officers at December 31, 2014.

Outstanding Equity Awards At December 31, 2014

		Option Awards				Stock Awards	
Name	Grant Date	Number of Securities Underlying Unexercised Options (#) Exercisable[1]	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested[2]	Market Value of Shares or Units of Stock that Have Not Vested[3] ($)
Stanley T. Crooke	1/4/2010	109,163	--	$ 11.27	1/3/2017	--	--
	1/3/2011	119,552	2,544	$ 10.29	1/2/2018	--	--
	1/3/2012	78,169	29,034	$ 7.25	1/2/2019	--	--
	1/30/2013	63,815	69,365	$ 14.69	1/29/2020	--	--
	1/2/2014	--	187,500	$ 39.87	1/1/2021	--	--
	1/15/2012	--	--	--	--	5,954	$ 367,600
	1/30/2013	--	--	--	--	16,642	$ 1,027,477
	1/15/2014	--	--	--	--	31,250	$ 1,929,375
Elizabeth L. Hougen	1/2/2009	12,657	--	$ 14.47	1/1/2016	--	--
	1/4/2010	20,000	--	$ 11.27	1/3/2017	--	--
	1/3/2011	21,541	459	$ 10.29	1/2/2018	--	--
	1/3/2012	14,218	5,282	$ 7.25	1/2/2019	--	--
	1/2/2013	7,522	8,178	$ 10.82	1/1/2020	--	--
	1/2/2013	3,593	3,907	$ 10.82	1/1/2020	--	--
	1/2/2014	—--	45,000	$ 39.87	1/1/2021	--	--
	1/15/2012	--	--	--	--	1,082	$ 66,803
	1/15/2013	--	--	--	--	937	$ 57,850
	1/15/2013	--	--	--	--	1,961	$ 121,072
	1/15/2014	--	--	--	--	1,082	$ 66,803
B. Lynne Parshall	1/3/2011	6,074	1,519	$ 10.29	1/2/2018	--	--
	1/3/2012	5,146	16,724	$ 7.25	1/2/2019	--	--
	1/30/2013	27,332	32,438	$ 14.69	1/29/2020	--	--
	1/2/2014	0	82,500	$ 39.87	1/2/2021	--	--
	1/15/2012	--	--	--	--	3,430	$ 211,768
	1/30/2013	--	--	--	--	7,785	$ 480,646
	1/30/2014	--	--	--	--	13,750	$ 848,925

		Option Awards				Stock Awards	
Name	Grant Date	Number of Securities Underlying Unexercised Options (#) Exercisable[1]	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested[2]	Market Value of Shares or Units of Stock that Have Not Vested[3] ($)
Brett P. Monia	1/3/2011	7,129	471	$ 10.29	1/2/2018	--	--
	1/1/2012	5,468	2,032	$ 7.21	12/31/2018	--	--
	1/3/2012	3,849	5,144	$ 7.25	1/2/2019	--	--
	1/30/2013	16,291	17,709	$ 14.69	1/29/2020	--	--
	1/2/2014	0	45,000	$ 39.87	1/1/2021	--	--
	1/15/2012	--	--	--	--	1,054	$ 65,074
	1/15/2012	--	--	--	--	416	$ 25,684
	1/30/2013	--	--	--	--	4,245	$ 262,086
	1/15/2014	--	--	--	--	7,500	$ 463,050
Richard S. Geary	1/4/2010	80	--	$ 11.27	1/3/2017	--	--
	1/3/2011	7,729	697	$ 10.29	1/2/2018	--	--
	1/3/2012	6,470	7,565	$ 7.25	1/2/2019	--	--
	1/30/2013	7,771	17,469	$ 14.69	1/29/2020	--	--
	1/2/2014	0	45,000	$ 39.87	1/1/2021	--	--
	1/15/2012	--	--	--	--	1,551	$ 95,759
	1/30/2013	--	--	--	--	4,192	$ 258,814
	1/15/2014	--	--	--	--	7,500	$ 463,050

(1) The options have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

(2) The RSUs were granted out of our 2011 Equity Incentive Plan. The RSUs vest at the rate of 25% per year over four years.

(3) Market value of stock awards was determined by multiplying the number of unvested shares by $61.74, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2014, the last trading day of fiscal 2014.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2014, certain information regarding option exercises and stock awards vesting during the last fiscal year with respect to our named executive officers:

	Option Awards		Stock Awards	
Name	Number of Shares Acquired on Exercise (#) (1)	Value Realized on Exercise ($)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting ($)
Stanley T. Crooke	10,000 3,000 13,000 20,000 15,500 15,000 5,000 3,000 2,500 3,000 2,000 11,000 10,000 7,000 11,000 4,000 25,000	$ 309,500 $ 83,250 $ 325,221 $ 468,820 $ 325,252 $ 240,825 $ 105,200 $ 63,240 $ 52,950 $ 63,390 $ 42,220 $ 226,941 $ 189,850 $ 204,246 $ 281,402 $ 102,120 $ 619,575	8,526	$ 406,349
Elizabeth L. Hougen	- -	- -	1,509	$ 71,919
B. Lynne Parshall(2)	2,510 3,972 8,561 443 15,875 10,628 23,635 31,028	$ 76,382 $ 149,097 $ 324,214 $ 14,615 $ 684,435 $ 318,318 $ 947,149 $ 1,195,105	4,310	$ 205,415
Brett Monia	15,000 2,344 10,000	$ 417,810 $ 62,993 $ 308,940	2,151	$ 102,517
Richard S. Geary	8,300 7,400 13,900 7,600	$ 293,455 $ 203,966 $ 594,864 $ 241,148	2,174	$ 103,613

(1) Each individual executed each option exercise and resulting sales pursuant to the individual's Rule 10b5-1 trading plan.

(2) Includes options exercised by Ms. Parshall's daughters and son-in-law.

Post-Employment Compensation

Pension Benefits and Nonqualified Deferred Compensation

We do not provide pension arrangements or post-retirement health coverage for our executives or employees. Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2014, we contributed to each participant a matching contribution equal to 25% of the first 6% of the participant's compensation that has been contributed to the plan. In 2014, the maximum matching contribution was $5,850. In 2015, we will contribute to each participant a matching contribution of 50% of the first 6% of the participant's compensation that has been contributed to the plan. We do not provide any nonqualified defined contribution or other deferred compensation plans.

Employment Agreements

All of our employees, including our executive officers, are employees-at-will and as such do not have employment contracts with us, except in the case of some severance agreements, the details of which are provided below.

Retention and Change of Control Agreements

In December 2008, we amended and restated our severance agreements with Stanley T. Crooke and B. Lynne Parshall to clarify the provisions of such agreements in light of Section 409A of the Code.

Specifically, these severance agreements provide the following severance benefits:

- Dr. Crooke will be eligible to receive a lump sum severance payment equal to 36 months of his then-current base salary in the event his employment is terminated as a result of a change of control of Isis; and
- Ms. Parshall will be eligible to receive a lump sum severance payment equal to:
  - 18 months of her then-current base salary in the event that her employment is terminated without cause; and
  - 30 months of her then-current base salary in the event that her employment is terminated as a result of a change of control of Isis.

These agreements will remain in effect as long as each individual continues to be employed by Isis.

In addition, the Compensation Committee has approved that in the event of a change of control, the vesting and exercisability of Dr. Crooke and Ms. Parshall's then outstanding and unvested stock options and RSUs will be accelerated in full, to the extent permitted by the applicable stock option plan.

Conditions

As a condition to receiving payments under each of the retention and change of control agreements described above, the officer is required to return all of our property and information and sign an agreement releasing Isis from liability.

Potential Payments Upon Termination or Change-of-Control

The following table estimates the lump sum payments that would be required under the agreements described above that were effective as of December 31, 2014. This table estimates the lump sum payments based upon either a termination without cause or a termination in connection with a change of control assuming either occurred on December 31, 2014. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 2 of this Form 10-K.

	Termination Event	
Name	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	--	$ 2,304,756
B. Lynne Parshall	$ 996,044	$ 1,660,073

Director Compensation

We pay our non-employee Directors a base fee of $50,000 with additional role-based compensation as noted below:

Role	2014 Cash Compensation
Board Member (Base)	$ 50,000
Committee Chairs (Additional)	
Audit	$ 24,000
Compensation	$ 15,000
Nominating & Gov.	$ 10,000
Agenda	$ 10,000
Committee Member (Additional)	
Audit	$ 10,000
Compensation	$ 7,500
Nominating & Gov.	$ 5,000
Agenda	$ 5,000
Scientific/Medical	$ 10,000

If the Board creates new committees, we anticipate that the non-employee members of such new committee will receive additional compensation for their role on those committees. We do not pay Board members additional compensation for attending Board meetings, but we do reimburse them for the expenses they incur to attend the meetings.

In 2014, each non-employee Director also received automatic stock award grants under our Directors' Plan. On July 1, 2014, under the Directors' Plan, each of our non-employee Directors serving at that time received an option to purchase 16,000 shares of our common stock, at an exercise price of $35.53 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on the Nasdaq Global Select Market, and an RSU for 2,667 shares. The options and RSUs vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2014 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2014

Name	Fees Earned or Paid in Cash ($)	Stock Awards ($)	Option Awards ($)[1]	All Other Compensation ($)	Total ($)
Spencer R. Berthelsen	$ 85,000	$ 94,759	$ 316,388	--	$ 496,147
Breaux B. Castleman	$ 60,000	$ 94,759	$ 316,388	--	$ 471,147
Joseph Klein	$ 60,000	$ 94,759	$ 316,388	--	$ 471,147
Joseph Loscalzo [2]	$ 65,000	$ 278,846	$ 932,098	--	$ 1,275,944
Frederick T. Muto	$ 55,000	$ 94,759	$ 316,388	--	$ 466,147
Joseph H. Wender	$ 86,500	$ 94,759	$ 316,388	--	$ 497,647

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to the Directors. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5, *Stockholders' Equity*, of the consolidated financial statements in this Form 10-K regarding assumptions underlying valuation of equity awards.

(2) Includes an option to purchase 22,500 shares of our common stock and an RSU for 3,750 shares of our common stock, which were automatically granted to Dr. Loscalzo under the Directors' Plan when he joined our Board.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2014, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards At December 31, 2014

	Option Awards				Stock Awards	
Name	Number of Securities Underlying Unexercised Options (#) Exercisable[1]	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested[2] [3]	Market Value of Shares or Units of Stock that Have Not Vested [4] ($)
Spencer R. Berthelsen	10,000	0	$ 3.95	6/30/15	4,697	$ 289,993
	12,500	0	$ 5.93	7/2/16		
	12,500	0	$ 9.77	7/1/17		
	15,000	0	$ 13.88	6/30/18		
	15,000	0	$ 16.32	6/30/19		
	15,000	0	$ 9.22	6/30/20		
	11,250	3,750	$ 9.30	6/30/21		
	5,626	5,624	$ 12.94	7/1/22		
	2,813	8,437	$ 28.47	6/30/23		
	0	16,000	$ 35.53	6/30/24		
Breaux B. Castleman	5,625	16,875	$ 26.66	6/24/23	6,885	$ 425,080
	2,813	8,437	$ 28.47	6/30/23		
	0	16,000	$ 35.53	6/30/24		
Joseph Klein	3,750	0	$ 9.22	6/30/20	4,697	$ 289,993
	3,750		$ 9.30	6/30/21		
	2,813	5,624	$ 12.94	7/1/22		
	2,813	8,437	$ 28.47	6/30/23		
	0	16,000	$ 35.53	6/30/24		
Joseph Loscalzo	0	22,500	$ 49.09	2/2/24	6,417	$ 396,186
	0	16,000	$ 35.53	6/30/24		
Frederick T. Muto	10,000	0	$ 3.95	6/30/15	4,697	$ 289,993
	12,500	0	$ 5.93	7/2/16		
	12,500	0	$ 9.77	7/1/17		
	15,000	0	$ 13.88	6/30/18		
	15,000	0	$ 16.32	6/30/19		
	15,000	0	$ 9.22	6/30/20		
	11,250	3,750	$ 9.30	6/30/21		
	5,626	5,624	$ 12.94	7/1/22		
	2,813	8,437	$ 28.47	6/30/23		
	0	16,000	$ 35.53	6/30/24		
Joseph H. Wender	10,000	0	$ 3.95	6/30/15	4,697	$ 289,993
	12,500	0	$ 5.93	7/2/16		
	12,500	0	$ 9.77	7/1/17		
	15,000	0	$ 13.88	6/30/18		
	15,000	0	$ 9.22	6/30/20		
	11,250	3,750	$ 9.30	6/30/21		
	5,626	5,624	$ 12.94	7/1/22		
	2,813	8,437	$ 28.47	6/30/23		
	0	16,000	$ 35.53	6/30/24		

(1) The options were granted out of our Directors' Plan and have a term of ten years and vest at the rate of 25% per year over four years.

(2) The RSUs were granted out of our Directors' Plan and vest at the rate of 25% per year over four years.

(3) All of our non-employee Directors are subject to our Stock Holding and Ownership Guidelines for RSU Shares, which requires each non-employee Director to accumulate and maintain shares of Common Stock issued pursuant to RSUs until he has accumulated shares of Common Stock equal to four times such non-employee Director's base annual cash retainer for service as a Director (but not for service on a Board committee), or until his termination of service.

(4) Market value of stock awards was determined by multiplying the number of unvested shares by $61.74, which was the closing market price of our common stock on the Nasdaq Select Market on December 31, 2014, the last trading day of fiscal 2014.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2014, certain information regarding option exercises and stock awards vested during the last fiscal year with respect to all of our non-employee Directors:

Option Exercises and Stock Vested in Fiscal 2014

	Option Awards		Stock Awards	
Name	Number of Shares Acquired on Exercise (#)	Value Realized on Exercise ($)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting ($)
Spencer R. Berthelsen	10,000	$ 282,900	782	$ 27,728
Breaux B. Castleman	--	--	1,407	$ 49,991
Joseph Klein, III	10,313	$ 343,039	782	$ 27,728
Frederick T. Muto	10,000	$ 228,700	782	$ 27,728
Joseph H. Wender	10,000	$ 418,437	782	$ 27,728
Joseph Loscalzo	--	--	--	--

Compensation Committee Interlocks and Insider Participation

During the fiscal year ended December 31, 2014, our Compensation Committee was composed of Dr. Berthelsen and Mr. Wender. None of the members of the Compensation Committee has ever been an employee or officer of Isis. None of our executive officers serves as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving as a member of our Board or Compensation Committee.

COMPENSATION COMMITTEE REPORT*

The Compensation Committee has:

- reviewed and discussed the Compensation Discussion and Analysis included in this Form 10-K with management; and
- based on this review and discussion, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in this Form 10-K.

The Compensation Committee
Spencer R. Berthelsen, *Chairman*
Joseph H. Wender

* This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the Securities Act or the Exchange Act.

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

Security Ownership of Certain Beneficial Owners and Management

This table outlines the ownership of our common stock as of February 18, 2015 by:

- each Director;
- each executive officer named in the Summary Compensation Table under "Executive Compensation--Compensation of Executive Officers";
- all Directors and executive officers as a group; and
- every entity that we know beneficially owns more than five percent of our common stock.

	Beneficial Ownership[1]	
Beneficial Owner	**Number of Shares**	**Percent of Total[2]**
FMR LLC[3] 245 Summer Street Boston, MA 02210	17,892,555	15.04
BlackRock, Inc.[4] 55 East 52nd Street New York, NY 10022	9,541,651	8.02
ClearBridge Investments, LLC[5] 620 8th Avenue New York, NY 10018	9,034,520	7.59
The Vanguard Group[6] 100 Vanguard Boulevard Malvern, PA 19355	7,271,871	6.11
BB Biotech AG[7] Vordergasse 3 CH-8200 Schaffhausen, Switzerland	5,976,526	5.02
Spencer R. Berthelsen[8]	150,154	*
Breaux B. Castleman[9]	9,845	*
Stanley T. Crooke[10]	1,198,094	1.0
Joseph Klein, III[11]	14,321	*
Joseph Loscalzo[12]	6,563	*
Frederick T. Muto[13]	102,284	*
B. Lynne Parshall[14]	73,060	*
Joseph H. Wender[15]	111,906	*
Brett Monia[16]	56,738	*
Richard S. Geary[17]	49,501	*
Elizabeth L. Hougen[18]	100,998	*
All Directors and executive officers as a group (fourteen persons)[19]	2,066,615	1.7

*Less than one percent

(1) We base this table upon information supplied by officers, Directors, principal stockholders and Form 3s, Form 4s, Form 5s, Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.

(2) Applicable percentages are based on 118,974,465 shares of common stock outstanding on February 18, 2015, adjusted as required by rules promulgated by the SEC.

(3) Abigail P. Johnson is a Director, the Vice Chairman, the Chief Executive Officer and the President of FMR LLC. Members of the family of Edward C. Johnson 3d, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC.

Neither FMR LLC nor Edward C. Johnson 3d nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act ("Fidelity Funds") advised by Fidelity Management & Research Company ("FMR Co"), a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds' Boards of Trustees. Fidelity Management & Research Company carries out the voting of the shares under written guidelines established by the Fidelity Funds' Boards of Trustees.

(4) Various persons at BlackRock, Inc. have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of shares of our common stock.

(5) ClearBridge Advisors, LLC, is an investment adviser registered under the Investment Advisers Act. ClearBridge Advisors has sole voting power to direct the vote of 8,778,431 shares and sole power to dispose or direct the disposition of 9,034,520 shares.

(6) The Vanguard Group has sole voting power to direct the vote of 158,221 shares, sole power to dispose or direct the disposition of 7,124,050 shares, and shared dispositive power for 147,821 shares. Vanguard Fiduciary Trust Company , a wholly-owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 147,821 shares or 0.12% of the Common Stock outstanding of Isis as a result of its serving as investment manager of collective trust accounts. Vanguard Investments Australia, Ltd., a wholly-owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 10,400 shares of Isis' Common Stock outstanding as a result of its serving as investment manager of Australian investment offerings.

(7) BB Biotech AG shares voting and dispositive powers with its wholly owned subsidiary, Biotech Target N.V.

(8) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 99,689 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 19, 2015.

(9) Includes 8,438 shares of common stock issuable upon exercise of options held by Mr. Castleman that are exercisable on or before April 19, 2015.

(10) Includes shares of common stock held by Dr. Crooke and 411,868 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 19, 2015. Also includes 1,297 shares of common stock and 44,896 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, which are exercisable on or before April 19, 2015. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.

(11) Includes 100 shares of common stock beneficially owned by Mr. Klein's son and 13,126 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before April 19, 2015.

(12) Includes 5,625 shares of common stock issuable upon exercise of options held by Mr. Loscalzo that are exercisable on or before April 19, 2015.

(13) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 99,689 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 19, 2015.

(14) Includes 64,988 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 19, 2015.

(15) Includes 74,689 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 19, 2015.

(16) Includes 52,312 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 19, 2015.

(17) Includes 41,931 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before April 19, 2015.

(18) Includes 100,998 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 19, 2015.

(19) Includes an aggregate of 1,194,610 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before April 19, 2015.

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, 2014.

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)	7,122,771	$	$19.69	3,208,151(c)
Equity compensation plans not approved by stockholders(b)	256,176	$	14.75	-
Total	7,378,947	$	19.52	3,208,151

(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 Employee Stock Purchase Plan, or 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, 370,136 remained available for purchase under the ESPP as of December 31, 2014. 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, 2014, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 256,176 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 5,280,021 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

Certain Relationships and Related Transactions

We have provided some of the information below because our stockholders may find it useful, but by including a transaction in this section, we do not necessarily mean that the transaction qualifies as a related party transaction under the securities laws.

Dr. Rosanne Crooke, the wife of Dr. Stanley Crooke, our Chairman and Chief Executive Officer, is a non-executive officer of Isis working part time at 30 hours per week. The Compensation Committee approves Dr. Rosanne Crooke's compensation. Her compensation is commensurate with the compensation of other employees at the same level at Isis. For the fiscal years ended 2014, 2013, and 2012, she received the following compensation:

Name and Principal Position	Year	Salary ($)	Bonus[1] ($)	Stock Awards[2] ($)	Option Awards[2][4] ($)	All Other Compensation[3] ($)	Total ($)
Rosanne Crooke Vice President, Cardiovascular Diseases Drug Discovery Research	2014	$ 210,814	$ 82,349	$ 67,487	$ 146,488	$ 5,912	$ 513,050
	2013	$ 203,685	$ 89,367	$ 23,457	$ 48,906	$ 3,777	$ 369,192
	2012	$ 197,369	$ 59,211	$ 9,622	$ 36,692	$ 4,517	$ 307,411

(1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2015 we paid bonuses for 2014 performance.

(2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to Dr. Crooke. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5, *Stockholders' Equity*, regarding assumptions underlying valuation of equity awards.

(3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.

(4) These amounts represent the estimated fair values of stock option grants we recognized as share-based compensation expense. The estimated fair value amounts were determined using the Black-Scholes option-valuation model and are not indicative of whether Dr. Rosanne Crooke will realize the estimated fair value or any financial benefits from the award. The applicable amounts represent:

- 11,404 shares at $7.25 per share received on January 3, 2012;
- 10,000 shares at $10.82 per share received on January 2, 2013; and
- 8,500 shares at $39.87 per share received on January 2, 2014.

One of our Directors, Mr. Muto, who was elected to the Board in March 2001, is a partner at Cooley LLP, our outside legal counsel. We paid Cooley LLP an aggregate of $425,119 in fees in 2014 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2014 fiscal year.

We have entered into indemnity agreements with each of our executive officers and Directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or Director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a Director, officer or other agent of Isis, and otherwise to the fullest extent permitted under Delaware law and our bylaws. Our bylaws provide that we will indemnify our Directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a Director or executive officer in connection with any proceeding initiated by such Director or executive officer.

Policies and Procedures Regarding Related Party Transactions

A committee of the Board composed entirely of independent Directors approves transactions with related persons, as defined under SEC regulations. The Compensation Committee of the Board approves all compensation we pay to employees that may qualify as a related person and the Audit Committee approves all other related party transactions, as specified in its charter. The committees only approve related-party transactions at committee meetings, or by unanimous written consent in lieu of a meeting, and record the approvals in the minutes of the committee.

For transactions that do not qualify as related party transactions, but may otherwise present a conflict of interest, our Code of Ethics and Business Conduct requires the Board (for our executive officers and Directors) or the Chief Executive Officer or Chief Operating Officer (for non-executive officers) to determine that no conflict of interest exists.

Our written policies and procedures specifically prohibit personal loans to our executive officers and any officer with a title of Vice President or higher.

Independence of the Board

As required under The Nasdaq Global Select Market listing standards, a majority of the members of a listed company's board of directors must qualify as "independent," as affirmatively determined by our Nominating, Governance and Review Committee of the Board. Our Nominating, Governance and Review Committee consults with our legal counsel to ensure that the Board's determinations are consistent with all relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in the applicable the Nasdaq Global Select Market listing standards and applicable SEC rules and regulations, as in effect from time to time.

Consistent with these considerations, after review of all relevant transactions or relationships between each Director, or any of his or her family members, and Isis, its senior management and its independent auditors, the Board affirmatively has determined that all of our Directors are independent Directors within the meaning of the applicable the Nasdaq Select Market listing standards and SEC rules and regulations, except for Dr. Crooke and Ms. Parshall, our Chief Executive Officer and Chief Operating Officer, respectively. In making this determination, the Board found that none of these Directors or nominees for Director has a material or other disqualifying relationship with us. With respect to Mr. Muto who is a partner of Cooley LLP, our outside legal counsel, he is independent for purposes other than serving on the Audit Committee or Compensation Committee, of which he is not a member.

Item 14. Principal Accounting Fees and Services

Independent Auditors' Fees

The Audit Committee has adopted a policy and procedure for the pre-approval of audit and permissible non-audit services rendered by our independent registered public accounting firm, Ernst & Young LLP. The policy generally pre-approves specific services in the defined categories of audit services, audit-related services, and tax services up to pre-determined amounts. The Audit Committee may pre-approve services as part of its approval of the scope of the engagement of the independent auditor or on an individual explicit case-by-case basis before the Audit Committee engages the independent registered public accounting firm to provide each service. As an additional measure to ensure auditor independence, we do not use Ernst & Young LLP as our primary tax advisor. The Audit Committee pre-approved the fees described below.

Audit Fees

For the fiscal years ended December 31, 2014 and 2013, Ernst & Young LLP billed us $0.6 million for each year, primarily related to the integrated audit of our financial statements and reviews of our interim financial statements. In addition, Ernst & Young LLP billed us $0.1 million in 2014 related to our convertible debt offering in November 2014. Furthermore, Ernst & Young LLP billed us $0.1 million in 2013 in connection with our public offering of common stock in May 2013.

Audit Related Fees

For the years ended December 31, 2014 and 2013, there were no audit related fees billed by Ernst & Young.

Tax Fees

For the years ended December 31, 2014 and 2013, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees.

All Other Fees

During the fiscal years ended December 31, 2014 and 2013, all other fees billed by Ernst & Young LLP were $1,995 each year. These fees were for a subscription to an online accounting and tax information service.

The Audit Committee has determined that the rendering of all non-audit services by Ernst & Young LLP is compatible with maintaining the auditor's independence.

During the fiscal year ended December 31, 2014, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's employees.

PART IV

Item 15. Exhibits, 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 146.

(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 27th day of February, 2015.

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 27, 2015
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer and Secretary	February 27, 2015
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 27, 2015
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 27, 2015
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	February 27, 2015
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 27, 2015
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	February 27, 2015
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 27, 2015
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 27, 2015

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 June 17, 2014. (42)
3.3	Amended and Restated Bylaws. (13)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock. (12)
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. (30)
4.5	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021. (41)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule. (37)
10.2*	Registrant's 1989 Stock Option Plan, as amended. (27)
10.3*	Registrant's Amended and Restated Employee Stock Purchase Plan. (15)
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. (24)
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. (14)
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. (10)

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. (24)
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. (17)
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. (25)
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. (10)
10.16	Registrant's Amended and Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 12, 2013. (34)
10.17*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. (42)
10.18*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement. (21)
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. (32)
10.20*	Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. (16)
10.21*	Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and B. Lynne Parshall. (16)
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. (20)
10.23*	Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (19)
10.24	Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc. (23)
10.25*	Form of Option Agreement for Options granted under the 2011 Equity Incentive Plan. (29)
10.26*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan. (29)
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. (25)
10.28*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan. (11)
10.29*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan. (11)
10.30*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan. (11)
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. (25)
10.32	First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009. (24)
10.33	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC. (18)

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. (23)

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. (24)

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. (26)

10.39 Second Amendment to Loan Agreement dated November 15, 2010 between the Registrant and RBS Asset Finance, Inc. (22)

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. (31)

10.41 Third Amendment to Loan Agreement dated June 24, 2012 between the Registrant and RBS Asset Finance, Inc. (32)

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. (32)

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. (33)

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. (37)

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. (37)

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. (37)

10.47 HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (35)

10.48 Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (35)

10.49 Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated September 5, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

10.50 Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

10.51 Amendment Number Three to the Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated August 2, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

10.52 Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (38)

10.53 Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (39)

10.54 Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (39)

10.55 Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (39)

10.56 Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (40)

10.57	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (40)
10.58	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (40)
10.59	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.60	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014. Portions of this exhibit have been omitted and separately filed with the SEC.
10.61	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014. 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. (36)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney. (28)
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. (8)
101	The following financial statements from the Isis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2014, 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, 2009, 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 Notice of 2011 Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 28, 2011, and incorporated herein by reference.

(20) 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.

(21) 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.

(22) 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.

(23) 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.

(24) 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.

(25) 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.

(26) 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.

(27) 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.

(28) Filed as part of the Annual Report on Form 10-K for the year ended December 31, 2013, and incorporated herein by reference.

(29) 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.

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

(32) 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.

(33) 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.

(34) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.

(35) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference.

(36) Filed as an exhibit to the Registrant's Report on Form 8-K filed on December 9, 2013 and incorporated herein by reference.

(37) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference.

(38) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 and incorporated herein by reference.

(39) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference.

(40) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference.

(41) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 17, 2014 and incorporated herein by reference.

(42) Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, 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, 2014 and 2013, 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, 2014. 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, 2014 and 2013, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, 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, 2014, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 27, 2015 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 27, 2015

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

	December 31,	
	2014	2013
ASSETS		
Current assets:		
Cash and cash equivalents	$ 142,998	$ 159,973
Short-term investments	585,834	496,788
Contracts receivable	3,903	11,102
Inventories	6,290	8,033
Investment in Regulus Therapeutics Inc.	81,881	52,096
Other current assets	15,691	7,518
Total current assets	836,597	735,510
Property, plant and equipment, net	88,958	86,198
Licenses, net	2,690	4,572
Patents, net	17,186	15,517
Deposits and other assets	10,378	5,359
Total assets	$ 955,809	$ 847,156
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 17,984	$ 11,009
Accrued compensation	12,302	12,168
Accrued liabilities	30,451	22,092
Current portion of long-term obligations	2,882	4,408
Current portion of deferred contract revenue	51,713	48,135
Total current liabilities	115,332	97,812
Long-term deferred contract revenue	127,797	142,790
1 percent convertible senior notes	327,486	—
2¾ percent convertible senior notes	48,014	150,334
Long-term obligations, less current portion	7,669	6,542
Long-term financing liability for leased facility	71,731	71,288
Total liabilities	698,029	468,766
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 118,442,726 and 116,471,371 shares issued and outstanding at December 31, 2014 and December 31, 2013, respectively	118	116
Additional paid-in capital	1,224,509	1,324,804
Accumulated other comprehensive income	39,747	21,080
Accumulated deficit	(1,006,594)	(967,610)
Total stockholders' equity	257,780	378,390
Total liabilities and stockholders' equity	$ 955,809	$ 847,156

See accompanying notes.

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

	Years Ended December 31,		
	2014	2013	2012
Revenue:			
Research and development revenue under collaborative agreements	$ 202,514	$ 144,194	$ 96,415
Licensing and royalty revenue	11,647	3,091	5,634
Total revenue	214,161	147,285	102,049
Expenses:			
Research, development and patent expenses	241,751	184,033	158,458
General and administrative	20,140	14,918	12,515
Total operating expenses	261,891	198,951	170,973
Loss from operations	(47,730)	(51,666)	(68,924)
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	—	—	(1,406)
Investment income	2,682	2,085	1,844
Interest expense	(22,209)	(19,355)	(21,152)
Gain on investments, net	1,256	2,378	1,465
Gain on investment in Regulus Therapeutics Inc.	19,902	—	18,356
Loss on early retirement of debt	(8,292)	—	(4,770)
Loss before income tax benefit	(54,391)	(66,558)	(74,587)
Income tax benefit	15,407	5,914	9,109
Net loss	$ (38,984)	$ (60,644)	$ (65,478)
Basic and diluted net loss per share	$ (0.33)	$ (0.55)	$ (0.65)
Shares used in computing basic and diluted net loss per share	117,691	110,502	100,576

See accompanying notes.

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

	Years Ended December 31,		
	2014	2013	2012
Net loss	$ (38,984)	$ (60,644)	$ (65,478)
Unrealized gains on investments, net of tax	40,079	10,253	13,250
Reclassification adjustment for realized gains included in net loss	(21,412)	(1,653)	—
Comprehensive loss	$ (20,317)	$ (52,044)	$ (52,228)

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2014, 2013 and 2012
(In thousands)

	Isis Pharmaceuticals, Inc. Stockholders' Equity					
	Common stock		Additional paid in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity
Description	Shares	Amount				
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), net of tax	—	—	—	13,250	—	13,250
Issuance of common stock in connection with employee stock plans	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 December 31, 2012	101,481	$ 102	$ 1,077,150	$ 12,480	$ (906,966)	$ 182,766
Net loss	—	—	—	—	(60,644)	(60,644)
Change in unrealized gains (losses), net of tax	—	—	—	8,600	—	8,600
Issuance of common stock in connection with employee stock plans	5,372	5	62,953	—	—	62,958
Issuance of public common stock	9,618	9	173,283	—	—	173,292
Share-based compensation expense	—	—	11,418	—	—	11,418
Balance at December 31, 2013	116,471	$ 116	$ 1,324,804	$ 21,080	$ (967,610)	$ 378,390
Net loss	—	—	—	—	(38,984)	(38,984)
Change in unrealized gains (losses), net of tax	—	—	—	18,667	—	18,667
Issuance of common stock in connection with employee stock plans	1,972	2	23,071	—	—	23,073
2¾ percent convertible senior notes repurchase, equity portion	—	—	(326,444)	—	—	(326,444)
1 percent convertible senior notes, equity portion, net of issuance costs	—	—	170,232	—	—	170,232
Share-based compensation expense	—	—	31,383	—	—	31,383
Excess tax benefits from share-based compensation awards	—	—	1,463	—	—	1,463
Balance at December 31, 2014	118,443	$ 118	$ 1,224,509	$ 39,747	$ (1,006,594)	$ 257,780

See accompanying notes.

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

	Years Ended December 31,		
	2014	2013	2012
Operating activities:			
Net loss	$ (38,984)	$ (60,644)	$ (65,478)
Adjustments to reconcile net loss to net cash provided by operating activities:			
Depreciation	6,380	6,591	7,074
Amortization of patents	1,142	1,184	1,224
Amortization of licenses	1,882	2,007	2,457
Amortization of premium on investments, net	7,470	5,572	4,193
Amortization of debt issuance costs	595	415	619
Amortization of 2⅝ percent convertible subordinated notes discount	—	—	6,169
Amortization of 2¾ percent convertible senior notes discount	6,723	6,344	2,268
Amortization of 1 percent convertible senior notes discount	2,256	—	—
Amortization of long-term financing liability for leased facility	6,622	6,567	6,503
Share-based compensation expense	31,383	11,418	8,571
Equity in net loss of Regulus Therapeutics Inc.	—	—	1,406
Gain on investment in Regulus Therapeutics Inc.	(19,902)	—	(18,356)
Loss on early retirement of debt	8,292	—	4,770
Gain on investments, net	(1,256)	(2,378)	(1,465)
Non-cash losses related to patents, licensing and property, plant and equipment	1,305	6,306	825
Tax benefit from other unrealized gains on securities	(12,835)	(5,914)	(9,111)
Changes in operating assets and liabilities:			
Contracts receivable	7,199	(10,580)	6,399
Inventories	1,743	(1,912)	(1,982)
Other current and long-term assets	(1,750)	(1,091)	279
Accounts payable	4,824	66	1,292
Income taxes	(4,034)	—	—
Accrued compensation	134	4,290	(1,305)
Deferred rent	153	217	255
Accrued liabilities	8,358	6,691	(3,254)
Deferred contract revenue	(11,415)	88,344	48,523
Net cash provided by operating activities	6,285	63,493	1,876
Investing activities:			
Purchases of short-term investments	(391,883)	(425,554)	(217,877)
Proceeds from the sale of short-term investments	294,727	172,762	242,659
Purchases of property, plant and equipment	(7,518)	(1,552)	(1,479)
Acquisition of licenses and other assets, net	(3,586)	(3,810)	(3,691)
Investment in Regulus Therapeutics Inc.	—	—	(3,000)
Purchases of strategic investments	—	—	(790)
Proceeds from the sale of Regulus Therapeutics, Inc.	22,949	—	—
Proceeds from the sale of strategic investments	2,463	2,428	2,177
Net cash (used in) provided by investing activities	(82,848)	(255,726)	17,999
Financing activities:			
Proceeds from equity awards	23,071	62,958	9,470
Proceeds from issuance of 2¾ percent convertible senior notes, net of issuance costs	—	—	194,697
Proceeds from issuance of 1 percent convertible senior notes, net of issuance costs	487,035	—	—
Principal and premium payment on redemption of the 2⅝ percent convertible subordinated notes	—	—	(163,718)
Repurchase of $140 million principal amount of the 2¾ percent convertible senior notes	(441,394)	—	—
Proceeds from public common stock offering	—	173,292	—
Proceeds from equipment financing arrangement	—	2,513	9,100
Excess tax benefits from share-based compensation awards	1,463	—	—
Principal payments on debt and capital lease obligations	(10,587)	(11,039)	(10,419)
Net cash provided by financing activities	59,588	227,724	39,130
Net (decrease) increase in cash and cash equivalents	(16,975)	35,491	59,005
Cash and cash equivalents at beginning of year	159,973	124,482	65,477
Cash and cash equivalents at end of year	$ 142,998	$ 159,973	$ 124,482

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

Supplemental disclosures of cash flow information:			
Interest paid	$ 6,353	$ 6,000	$ 5,770
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 2,151	$ 704	$ 647

See accompanying notes.

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, Akcea Therapeutics, Inc., which was formed in December 2014 to develop and commercialize the drugs in our lipid franchise.

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 net loss for the years ended December 31, 2014, 2013 and 2012, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 percent convertible senior notes;
- 2¾ percent convertible senior notes;
- 2⅝ percent convertible subordinated notes;
- GSK convertible promissory notes issued by Regulus;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

We issued 1 percent convertible senior notes in November 2014. We issued 2¾ percent convertible senior notes in August 2012, of which a portion was redeemed in conjunction with the issuance of our 1 percent notes. We redeemed all of our 2⅝ percent notes in September 2012. In October 2012 Regulus completed an IPO, after which we were no longer guarantors of the two convertible notes that Regulus issued to GSK. As a result, the 2⅝ percent notes and GSK convertible promissory notes were not common equivalent shares for the years ended December 31, 2014 and 2013.

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 the 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 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 stand-alone 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 global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the collaboration, we received a $25 million upfront payment in December 2012 and a $6 million payment in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. We also granted AstraZeneca options to license up to three cancer drugs under the separate research program. We were responsible for completing IND-enabling studies for ISIS-AR-2.5$_{Rx}$, which we completed in early 2014. We are also responsible for completing an ongoing clinical study of ISIS-STAT3-2.5$_{Rx}$, which we plan to complete in the first quarter of 2015. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. 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 when we entered into the agreement 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-STAT3-2.5$_{Rx}$ for the treatment of cancer;
- The development services we are performing for ISIS-STAT3-2.5$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AR-2.5$_{Rx}$ and the research services we performed for ISIS-AR-2.5$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we are performing for this program.

We determined that the ISIS-STAT3-2.5$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3-2.5$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3-2.5$_{Rx}$ 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 considered the ISIS-STAT3-2.5$_{Rx}$ license and the development services for ISIS-STAT3-2.5$_{Rx}$ to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3-2.5$_{Rx}$ license immediately because we delivered the license and earned the revenue. We are recognizing as revenue the amount allocated to the development services for ISIS-STAT3-2.5$_{Rx}$ over the period of time we perform services, which we expect will end during the first quarter of 2015. The ISIS-AR-2.5$_{Rx}$ license is also an exclusive license. At the inception of the agreement, ISIS-AR-2.5$_{Rx}$ was in an early stage of research. Therefore, we concluded that our knowledge and expertise with antisense technology was essential for AstraZeneca or another third party to successfully develop ISIS-AR-2.5$_{Rx}$. As a result, we determined that the ISIS-AR-2.5$_{Rx}$ license did not have stand-alone value and we combined the ISIS-AR-2.5$_{Rx}$ license and related research services into one unit of accounting. We recognized revenue for the combined unit of accounting over the period of time we performed services, which ended in the first quarter of 2014. 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 are recognizing revenue for the combined unit of accounting over the period of our performance.

We determined that the initial 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. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. 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 allocable consideration 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-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$ 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 $25 million upfront payment for the ISIS-STAT3-2.5$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3-2.5$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed 10 percent increase or decrease in the estimated selling price of the ISIS-STAT3-2.5$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3-2.5$_{Rx}$ license would change by approximately seven percent, or $0.8 million, 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 outlining 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. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations may change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize in future periods.

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. For example, since early 2012 we have entered into four collaboration agreements with Biogen Idec:

- 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 a Phase 2 clinical trial.

- 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.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen Idec to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen Idec exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug identified during the six year term of this collaboration, while Biogen Idec is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen Idec the option 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 research and/or 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 all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements 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 four 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 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 we or our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered 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 us or 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 immediately. 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 access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen Idec substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we considered milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provided Alnylam ongoing access to our technology to develop and commercialize RNA interference, or RNAi, therapeutics. 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 in 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 do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. We consider most milestone payments 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. 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. For example, during 2014, we recognized $9.5 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Research, development and patent expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our consolidated balance sheet and we expense them as the services are provided. For the years ended December 31, 2014, 2013 and 2012, research and development expenses were $238.9 million, $173.7 million and $154.6 million, respectively. A portion of the costs included in research and development expenses are costs associated with our collaboration agreements. For the years ended December 31, 2014, 2013 and 2012, research and development costs of approximately $85.6 million, $51.0 million and $38.5 million, respectively, were related to our collaborative agreements.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, 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 10.1 years at December 31, 2014.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2014 and 2013 was $25.0 million and $24.9 million, respectively. Accumulated amortization related to patents was $7.8 million and $9.4 million at December 31, 2014 and 2013, respectively.

Based on existing patents, estimated amortization expense related to patents in each of the next five years is as follows:

Years Ending December 31,	Amortization (in millions)
2015	$ 1.2
2016	$ 1.1
2017	$ 1.1
2018	$ 0.9
2019	$ 0.8

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. In 2014, 2013 and 2012, patent expenses were $2.9 million, $10.3 million and $3.9 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $1.3 million, $6.4 million and $0.8 million, respectively.

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 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, or 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 three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months 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 income (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 own stock in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At December 31, 2014 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 income (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. We hold one cost method investment. Realization of our equity position in this company is uncertain. When realization of our investment is uncertain, 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, 2014, 2013 or 2012. Total inventory was $6.3 million and $8.0 million as of December 31, 2014 and 2013, respectively.

Property, plant and equipment

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

	December 31,	
	2014	2013
Equipment and computer software	$ 49,772	$ 44,698
Building and building systems	48,521	48,132
Land improvements	2,853	2,846
Leasehold improvements	37,935	35,282
Furniture and fixtures	5,732	5,473
	144,813	136,431
Less accumulated depreciation	(66,053)	(60,431)
	78,760	76,000
Land	10,198	10,198
Total	$ 88,958	$ 86,198

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

Computer software and hardware	3 years
Other equipment	5-7 years
Furniture and fixtures	5-10 years
Manufacturing equipment	10 years
Building systems and improvements	10-25 years
Land improvements	20 years
Building	40 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 five years and 15 years. The cost of our licenses at December 31, 2014 and 2013 was $36.1 million and $36.2 million, respectively. Accumulated amortization related to licenses was $33.4 million and $31.6 million at December 31, 2014 and 2013, respectively. Based on existing licenses, estimated amortization expense related to licenses is as follows:

Years Ending December 31,	Amortization (in millions)
2015	$ 1.9
2016	$ 0.8

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 charges of $1.3 million, $6.4 million and $0.8 million for the years ended December 31, 2014, 2013 and 2012, 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 Regulus' IPO in October 2012. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. See Note 3, *Investments,* for additional information regarding our fair value accounting for our investment in Regulus. 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."

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, 2014 and 2013, we had collaborative arrangements with two and five entities, respectively, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have the power to direct the activities that most significantly impact the economic performance of our variable interest entities, 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, 2014, the total carrying value of our investments in variable interest entities was $81.9 million, and was related to our investment in Regulus. Our maximum exposure to loss related to our collaborative arrangement variable interest entities is limited to the carrying value of our investments.

Stock-based compensation expense

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 ESPP based on the estimated fair value of the award on the date of grant. 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 use the Black-Scholes model as our method of valuing option awards and stock purchase rights under our 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 our board of directors. The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four year period.

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

Accumulated other comprehensive income

Accumulated other comprehensive income is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income to our consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income for the years ended December 31, 2014, 2013 and 2012 (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Beginning balance accumulated other comprehensive income (loss)	$ 21,080	$ 12,480	$ (770)
Other comprehensive income before reclassifications, net of tax (1)	40,079	10,253	13,250
Amounts reclassified from accumulated other comprehensive income (2)	(21,412)	(1,653)	—
Net current period other comprehensive income	18,667	8,600	13,250
Ending balance accumulated other comprehensive income	$ 39,747	$ 21,080	$ 12,480

(1) Other comprehensive income includes income tax expense of $12.8 million, $5.9 million and $9.1 million for the years ended December 31, 2014 and 2013 and 2012, respectively.

(2) Included in gain on investments, net on our consolidated statement of operations.

Convertible debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent convertible notes, 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.

We assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing the debt discount over the life of the convertible 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.

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 our investment in equity securities in publicly-held biotechnology companies; 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 us to develop our own assumptions. Our Level 3 investments include our investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. We determine 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. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the years ended December 31, 2014 and 2013 there were no transfers between our Level 1 and Level 2 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

We measure the following major security types at fair value on a recurring basis. The following summary breaks down the fair-value hierarchy that we valued each security with at December 31, 2014 and 2013 (in thousands):

	At December 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 104,680	$ 104,680	$ —	$ —
Corporate debt securities (2)	372,002	—	372,002	—
Debt securities issued by U.S. government agencies (3)	109,855	—	109,855	—
Debt securities issued by the U.S. Treasury (4)	19,017	19,017	—	—
Debt securities issued by states of the United States and political subdivisions of the states (5)	105,033	—	105,033	—
Investment in Regulus Therapeutics Inc.	81,881	—	—	81,881
Total	$ 792,468	$ 123,697	$ 586,890	$ 81,881

	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 133,233	$ 133,233	$ —	$ —
Corporate debt securities (7)	407,897	—	407,897	—
Debt securities issued by U.S. government agencies (3)	64,432	—	64,432	—
Debt securities issued by the U.S. Treasury (3)	15,328	15,328	—	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	22,255	—	22,255	—
Investment in Regulus Therapeutics Inc.	52,096	52,096	—	—
Equity securities (6)	1,276	1,276	—	—
Total	$ 696,517	$ 201,933	$ 494,584	$ —

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

(2) $0.8 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

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

(4) $10.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(5) $9.3 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

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

(7) $13.1 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

At the beginning of 2013 our Level 3 investments consisted of our investments in the equity securities we owned of Regulus and Sarepta Therapeutics, Inc. which had a gross fair value of $44.4 million and $1.0 million, respectively, less a lack of marketability discount of $10.8 million and $0.3 million, respectively, for a net carrying value of $33.6 million and $0.7 million, respectively. In the first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. In the fourth quarter of 2013, we re-classified our investment in Regulus to a Level 1 investment because we were no longer subject to contractual trading restrictions on the Regulus shares we owned. In the first quarter of 2014, Achaogen completed an initial public offering. As a result, we stopped using the cost method of accounting for our equity investment in Achaogen and instead we began accounting for it at fair value. Until September 2014, the fair value of our investment in Achaogen included a lack of marketability discount because there were restrictions on when we could trade the securities. As such, we classified our Achaogen stock as a Level 3 investment. In September 2014, we reclassified our investment in Achaogen to a Level 1 investment because the contractual trading restrictions on the shares we owned ended. In November 2014, Regulus completed a public offering. As part of the offering, we sold shares of Regulus' common stock and became subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, our investment in Regulus included a lack of marketability discount and was classified as a Level 3 investment.

We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the years ended December 31, 2014 and 2013 (in thousands):

	Year Ended December 31,	
	2014	2013
Beginning balance of Level 3 investments	$ —	$ 34,350
Transfers into Level 3 investments	108,009	—
Total realized and unrealized gains and (losses):		
Included in gain on investments	—	(1,163)
Included in accumulated other comprehensive income (loss)	(24,897)	32,272
Transfers out of Level 3 investments	(1,231)	(65,419)
Cost basis of shares sold	—	(40)
Ending balance of Level 3 investments	$ 81,881	$ —

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects in exchange for the goods or services. This guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening retained earnings balance. We will adopt this guidance in our fiscal year beginning January 1, 2017. We are currently in the process of determining the adoption method as well as the effects the adoption will have on our consolidated financial statements and disclosures.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance requires us to perform interim and annual assessments to determine our ability to continue as a going concern within one year from the date that we issue our financial statements. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. We will adopt this guidance in our fiscal year beginning January 1, 2017. We do not expect this guidance to have any effect on our 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. 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.

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. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. We also recorded an $18.4 million gain in the fourth quarter of 2012 because of the increase in Regulus' valuation resulting from its IPO. During 2014, we sold 1.5 million shares of common stock, resulting in a $19.9 million gain. We have reflected these gains in a separate line on our consolidated statement of operations called "Gain on investment in Regulus Therapeutics Inc." As of December 31, 2014, we owned approximately 11 percent of Regulus' equity, with a carrying balance of $81.9 million on our consolidated balance sheet.

3. Investments

As of December 31, 2014, 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, 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, 2014:

One year or less	55%
After one year but within two years	31%
After two years but within three years	14%
Total	100%

As illustrated above, at December 31, 2014, 86 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At December 31, 2014, we had an ownership interest of less than 20 percent in one private company and two public companies with which we conduct business. The privately-held company is Atlantic Pharmaceuticals Limited and the publicly-traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately-held company under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

During 2014, we realized a gain on investments we sold of $21.2 million, consisting primarily of the $19.9 million gain we realized when we sold a portion of the stock we own in Regulus. During 2013, we recognized a $2.4 million net gain on investments related to the sale of stock in several satellite companies. During 2012, we recognized an $18.4 million gain because of the increase in Regulus' valuation resulting from its IPO. Our gain from Regulus in 2012 and 2014 is reflected in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc."

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

December 31, 2014	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 219,856	$ 89	$ (89)	$ —	$ 219,856
Debt securities issued by U.S. government agencies	47,496	7	(27)	—	47,476
Debt securities issued by the U.S. Treasury (1)	19,008	9	—	—	19,017
Debt securities issued by states of the United States and political subdivisions of the states (1)	45,196	19	(53)	—	45,162
Total securities with a maturity of one year or less	331,556	124	(169)	—	331,511
Corporate debt securities	152,730	16	(600)	—	152,146
Debt securities issued by U.S. government agencies	62,530	—	(151)	—	62,379
Debt securities issued by states of the United States and political subdivisions of the states	60,073	32	(234)	—	59,871
Total securities with a maturity of more than one year	275,333	48	(985)	—	274,396
Total available-for-sale securities	$ 606,889	$ 172	$ (1,154)	$ —	$ 605,907

December 31, 2014	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 12,477	$ 69,404	$ —	$ —	$ 81,881
Total equity securities	$ 12,477	$ 69,404	$ —	$ —	$ 81,881
Total available-for-sale and equity securities	$ 619,366	$ 69,576	$ (1,154)	$ —	$ 687,788

December 31, 2013	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 142,096	$ 75	$ (27)	$ —	$ 142,144
Debt securities issued by U.S. government agencies(1)	23,242	22	(16)	—	23,248
Debt securities issued by the U.S. Treasury	6,239	6	—	—	6,245
Debt securities issued by states of the United States and political subdivisions of the states	8,082	6	(28)	—	8,060
Total securities with a maturity of one year or less	179,659	109	(71)	—	179,697
Corporate debt securities	265,969	177	(393)	—	265,753
Debt securities issued by U.S. government agencies	41,308	3	(127)	—	41,184
Debt securities issued by the U.S. Treasury	9,062	21	—	—	9,083
Debt securities issued by states of the United States and political subdivisions of the states	14,186	37	(28)	—	14,195
Total securities with a maturity of more than one year	330,525	238	(548)	—	330,215
Total available-for-sale securities	$ 510,184	$ 347	$ (619)	$ —	$ 509,912

December 31, 2013	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 36,570	$ —	$ —	$ 52,096
Securities included in other current assets	1,538	618	—	(880)	1,276
Securities included deposits and other assets	625	—	—	—	625
Total equity securities	$ 17,689	$ 37,188	$ —	$ (880)	$ 53,997
Total available-for-sale and equity securities	$ 527,873	$ 37,535	$ (619)	$ (880)	$ 563,909

(1) Includes investments classified as cash equivalents on our consolidated balance sheet.

Investments we consider to be temporarily impaired at December 31, 2014 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	239	$ 242,124	$ (681)	$ 3,503	$ (8)	$ 245,627	$ (689)
Debt securities issued by U.S. government agencies	16	98,342	(178)	—	—	98,342	(178)
Debt securities issued by states of the United States and political subdivisions of the states	46	54,292	(237)	225	(50)	54,517	(287)
Total temporarily impaired securities	301	$ 394,758	$ (1,096)	$ 3,728	$ (58)	$ 398,486	$ (1,154)

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

The carrying value of our long-term obligations was as follows (in thousands):

	December 31,	
	2014	2013
1 percent convertible senior notes	$ 327,486	$ —
2¾ percent convertible senior notes	48,014	150,334
Long-term financing liability for leased facility	71,731	71,288
Equipment financing arrangement	3,226	7,461
Leases and other obligations	7,325	3,489
Total	$ 457,782	$ 232,572
Less: current portion	(2,882)	(4,408)
Total Long-Term Obligations	$ 454,900	$ 228,164

Convertible Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We raised $487 million, of proceeds, net of issuance costs. We used a substantial portion of the net proceeds from the issuance of the 1 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes at a price of $441.9 million, including accrued interest. As a result, the new principal balance of the 2¾ percent notes is $61.2 million. We recognized a $8.3 million non-cash loss as a result of the early retirement of a portion of the 2¾ percent notes.

In September 2012, we used a substantial portion of the net proceeds of $194.7 from the issuance of $201.3 million of 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. 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.

At December 31, 2014 we had the following convertible debt outstanding (amounts in millions unless otherwise noted):

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Outstanding balance	$ 500	$ 61.2
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually in arrears on May 15 and November 15 of each year for the 1 percent notes and on April 1 and October 1 for the 2 ¾ percent notes.

The 1 percent notes are convertible at the option of the note holders prior to July 1, 2021 only under certain conditions. On or after July 1, 2021, the notes are initially convertible into approximately 7.5 million shares of common stock at a conversion price of approximately $66.81 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 may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. If we undergo a fundamental change, holders may require us to purchase for cash all or any portion of their 1 percent notes at a purchase price equal to 100% of the principal amount of the notes to be purchased, plus accrued and unpaid interest to, but excluding, the fundamental change purchase date.

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 convertible into approximately 3.7 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.

For the 2¾ percent notes, the price of our common stock exceeded the conversion threshold price during the quarter ended December 31, 2014. As a result, the 2¾ percent notes are convertible at the option of the holders during the quarter ending March 31, 2015. As of December 31, 2014, the if-converted value of the 2¾ percent notes, which assumes that the notes will be converted into shares of our common stock, exceeded the principal amount by $166.2 million. 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 and to record the remaining portion in equity. As a result, we recorded our convertible notes at a discount, which we are amortizing as additional non-cash interest expense over the expected life of the respective debt. We determined our nonconvertible debt borrowing rate using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model. The following table summarizes the nonconvertible borrowing rate, effective interest and amortization period of our debt discount for our convertible notes:

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes	2⅝ Percent Convertible Subordinated Notes
Nonconvertible debt borrowing rate	7.4 percent	8.0 percent	9.3 percent
Effective interest rate	7.8 percent	8.8 percent	9.8 percent
Amortization period of debt discount	7 years	7 years	7 years

Interest expense for the year ended December 31, 2014, 2013 and 2012 included $9.6 million, $6.8 million and $9.8 million, respectively, of non-cash interest expense related to the amortization of the debt discount and debt issuance costs for our convertible notes.

The following table summarizes information about the equity and liability components of our outstanding convertible notes, (in thousands). The fair values of the convertible notes outstanding were measured based on quoted market prices, which is a Level 2 measurement:

	December 31,	
	2014	2013
2¾ Percent Convertible Senior Notes		
Fair value of outstanding notes	$ 223,900	$ 505,100
Principal amount of convertible notes outstanding	$ 61,247	$ 201,250
Unamortized portion of debt discount	$ 13,233	$ 50,916
Long-term debt	$ 48,014	$ 150,334
Carrying value of equity component	$ 18,714	$ 59,528
1 Percent Convertible Senior Notes		
Fair value of outstanding notes	$ 568,000	
Principal amount of convertible notes outstanding	$ 500,000	
Unamortized portion of debt discount	$ 172,514	
Long-term debt	$ 327,486	
Carrying value of equity component	$ 174,770	

Equipment Financing Arrangement

In October 2008, we entered into an equipment financing loan agreement, 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 and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.39 percent. As of December 31, 2014, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.18 percent. The carrying balance under this loan agreement at December 31, 2014 and 2013 was $3.2 million and $7.5 million, respectively.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2014 are as follows (in thousands):

2015	$ 9,446
2016	7,268
2017	6,744
2018	6,744
2019	67,991
Thereafter	511,020
Subtotal	$ 609,213
Less: current portion	(2,882)
Less: fixed and determinable interest	(44,222)
Less: unamortized portion of debt discount	(185,747)
Plus: Deferred rent	1,795
Total	$ 378,157

Operating Leases

We lease office and laboratory space under non-cancelable operating leases with terms through December 2031. We are located in three buildings in Carlsbad, California, which consists of laboratory and office space. Our facilities include a primary research and development facility, a manufacturing facility and a building adjacent to our manufacturing facility. Our manufacturing facility is used for our drug development business and was built to meet current Good Manufacturing Practices and the facility adjacent to our manufacturing facility has laboratory and office space that we use to support our manufacturing activities. The lease for our 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 facility adjacent to our manufacturing facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods. We account for the lease of our primary research and development facility as a financing obligation as discussed below. We also lease office equipment under non-cancelable operating leases with terms through June 2017.

Annual future minimum payments under operating leases as of December 31, 2014 are as follows (in thousands):

	Operating Leases
2015	$ 1,527
2016	1,538
2017	1,481
2018	1,451
2019	1,474
Thereafter	17,517
Total minimum payments	$ 24,988

Rent expense for the years ended December 31, 2014 and 2013 was $1.8 million for each year and for 2012 rent expense was $1.9 million. We recognize rent expense on a straight line basis over the lease term for the lease on our manufacturing facility and the lease on our building adjacent to our manufacturing facility, which resulted in a deferred rent balance of $1.8 million and $1.6 million at December 31, 2014 and 2013, respectively.

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P., or BioMed. Under the lease, BioMed constructed primary research and development facility in Carlsbad, California. The lease 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. 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 and began depreciating the cost of the facility over its economic useful life. At December 31, 2014 and 2013, the facility and associated parcel of land had a net book value of $64.4 million and $66.7 million, respectively, which included $7.7 million and $5.5 million, respectively, of accumulated depreciation. We are applying 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, 2014 and 2013 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.

Annual future rent payments as of December 31, 2014 for our primary research and development facility are as follows (in thousands):

	Future Rent Payments
2015	$ 6,179
2016	6,550
2017	6,550
2018	6,943
2019	6,943
Thereafter	98,565
Total minimum payments	$ 131,730

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, 2014, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2014.

Common Stock

At December 31, 2014 and 2013, we had 300,000,000 and 200,000,000 shares of common stock authorized, respectively, of which 118,442,726 and 116,471,371 were issued and outstanding, respectively. As of December 31, 2014, total common shares reserved for future issuance were 19,183,780.

In June 2013, we completed the sale of 9,617,869 shares of our common stock through a public offering at a price of $19.00 per share, which included 617,869 additional shares sold pursuant to an option we granted to the underwriters. We received net proceeds of approximately $173.3 million from the sale of these shares net of underwriting discounts and commissions and other estimated offering expenses of $9.5 million.

During the years ending December 31, 2014, 2013 and 2012, we issued 1,972,000, 5,372,000 and 1,438,000 shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of $23.1 million, $63.0 million and $9.5 million in 2014, 2013 and 2012, respectively.

Stock 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 2024. 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, on a monthly basis, 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, 2014, a total of 4,895,598 options were outstanding, of which options to purchase 3,291,939 shares were exercisable, and 7,269 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, on a monthly basis thereafter. At December 31, 2014, a total of 256,176 options were outstanding and 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 5,500,000 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 unit 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 have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four year period. At December 31, 2014, a total of 1,706,486 options were outstanding, of which none were exercisable, 605,493 restricted stock unit awards were outstanding, and 3,029,009 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, 2014, a total of 520,687 options were outstanding, of which 305,631 were exercisable, 32,090 restricted stock unit awards were outstanding, and 171,873 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 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 2,574,596 million shares authorized under the plan as of December 31, 2014. 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 that ended on January 1, 2010. During 2014, employees purchased and we issued to employees 44,139 shares under the ESPP at $26.85 per share. At December 31, 2014, 370,136 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, 2014 (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, 2013	7,279	$ 12.07		
Granted	2,031	$ 39.88		
Exercised	(1,816)	$ 12.36		
Cancelled/forfeited/expired	(115)	$ 20.43		
Outstanding at December 31, 2014	7,379	$ 19.52	4.41	$ 311,538
Exercisable at December 31, 2014	3,854	$ 11.18	3.22	$ 194,858

The weighted-average estimated fair values of options granted were $17.54, $7.10 and $3.55 for the years ended December 31, 2014, 2013 and 2012, respectively. The total intrinsic value of options exercised during the years ended December 31, 2014, 2013 and 2012 were $62.8 million, $69.6 million and $7.6 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $22.4 million, $62.0 million and $8.7 million for the years ended December 31, 2014, 2013 and 2012, respectively. For the year ended December 31, 2014, the weighted-average fair value of options exercised was $46.96. As of December 31, 2014, total unrecognized compensation cost related to non-vested stock-based compensation plans was $21.3 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 1.1 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2014 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2013	425	$ 13.67
Granted	349	$ 44.94
Vested	(117)	$ 13.74
Cancelled/forfeited	(19)	$ 22.41
Non-vested at December 31, 2014	638	$ 30.52

For the years ended December 31, 2014, 2013 and 2012, the weighted-average grant date fair value of RSUs granted was $44.94, $17.42 and $8.36 per RSU, respectively. As of December 31, 2014, total unrecognized compensation cost related to RSUs was $9.8 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 1.4 years.

Stock-based Valuation and Compensation Expense Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2014, 2013 and 2012 (in thousands), which was allocated as follows:

	Year Ended December 31,		
	2014	2013	2012
Research, development and patents	$ 25,843	$ 9,673	$ 7,246
General and administrative	5,540	1,745	1,325
Total	$ 31,383	$ 11,418	$ 8,571

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 our 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 actual and projected 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, 2014, 2013 and 2012, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2014	2013	2012
Risk-free interest rate	1.7%	1.1%	1.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	50.1%	51.1%	50.7%
Expected life	4.7 years	5.1 years	5.1 years

Board of Director Stock Options:

	December 31,		
	2014	2013	2012
Risk-free interest rate	2.2%	2.2%	1.3%
Dividend yield	0.0%	0.0%	0.0%
Volatility	54.2%	52.7%	51.3%
Expected life	6.9 years	7.2 years	7.6 years

ESPP:

	December 31,		
	2014	2013	2012
Risk-free interest rate	0.1%	0.1%	0.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	60.1%	62.9%	44.5%
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. We estimated the expected term of options we have granted based on actual and projected exercise patterns.

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.

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 carryforwards. 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, 2014. 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 2014, 2013 and 2012, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. In December 31, 2014, 2013 and 2012, we recorded a $12.8 million, $5.9 million and $9.1 million tax benefit, respectively, in continuing operations and a $12.8 million, $5.9 million and $9.1 million tax expense, respectively, in other comprehensive income.

In December, 2014, we reached an agreement with the State of California Franchise Tax Board with regard to California franchise tax we paid for the tax year ended December 31, 2009. As part of the agreement, we will receive a franchise tax refund of $4.3 million and our research credit carry-forward to December 31, 2010 will increase by $4.3 million. We recognized an income tax benefit for the refund in the fourth quarter of 2014. The increase in our research credit carry-forward will increase our deferred tax assets but will not impact our consolidated balance sheet as we record a full valuation allowance on our deferred tax assets.

We are subject to taxation in the United States and various state jurisdictions. Our tax years for 1998 and forward are subject to examination by the U.S. tax authorities and our tax years for 2001 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.

The provision for income taxes on income from continuing operations were as follows (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Current:			
Federal	$ 263	$ —	$ —
State	(4,295)	2	2
Total current	(4,032)	2	2
Deferred:			
Federal	(8,948)	(5,082)	(7,827)
State	(2,427)	(834)	(1,284)
Foreign	—	—	—
Total deferred	(11,375)	(5,916)	(9,111)
Income Tax Benefit	$ (15,407)	$ (5,914)	$ (9,109)

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,					
	2014		2013		2012	
Pre-tax loss	$ (54,391)		$ (66,558)		$ (74,587)	
Statutory rate	(19,035)	35.0%	(23,295)	35.0%	(26,105)	35.0%
State income tax net of federal benefit	(3,125)	5.7%	(3,823)	5.7%	(4,284)	5.7%
Net change in valuation allowance	29,547	(54.3)%	28,850	(43.3)%	25,269	(33.9)%
Gain on Investment in Regulus Therapeutics Inc.	—	—	—	—	(6,353)	8.5%
Loss on debt extinguishment	2,406	(4.4%)	—	—	—	—
Tax credits	(23,525)	43.3%	(15,839)	23.8%	806	(1.1)%
California franchise tax refund	(2,795)	5.1%	—	—	—	—
Deferred tax true-up	874	(1.6)%	8,023	(12.1)%	839	(1.1)%
Other	246	(0.5)%	170	(0.2)%	719	(0.9)%
Effective rate	$ (15,407)	28.3%	$ (5,914)	8.9%	$ (9,109)	12.2%

Significant components of our deferred tax assets and liabilities as of December 31, 2014 and 2013 are as follows (in thousands):

	Year Ended December 31,	
	2014	2013
Deferred Tax Assets:		
Net operating loss carryovers	$ 231,654	$ 260,462
R&D credits	93,594	65,600
Capitalized R&D	3,088	2,736
Deferred revenue	58,836	28,555
Accrued restructuring	2,374	3,304
Other	3,762	7,107
Total deferred tax assets	$ 393,308	$ 367,764
Deferred Tax Liabilities:		
Convertible debt	$ (73,733)	$ (20,895)
Intangible and capital assets	(3,641)	(4,614)
Net deferred tax asset	$ 315,934	$ 342,255
Valuation allowance	(315,934)	(342,255)
Net deferreds	$ —	$ —

The deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2014 and 2013 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 $49.5 million if and when we ultimately realize such deferred tax assets. We use the with and without approach for purposes of determining when excess tax benefits have been realized.

At December 31, 2014, we had federal and California tax net operating loss carryforwards of approximately $671.9 million and $888.7 million, respectively. Our federal tax loss carryforwards begin to expire in 2023. Our California tax loss carryforwards began to expire in 2014. At December 31, 2014, we also had federal and California research and development tax credit carryforwards of approximately $86.0 million and $34.5 million, respectively. Our Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless we use them prior to expiration. Our California research and development tax credit carryforwards are available indefinitely. In 2009, we had a substantial amount of taxable income and we used a portion of our Federal NOL carryforwards to reduce our federal income taxes. We did not use any of our California NOL carryforwards to offset our state taxes in 2009 because California suspended the use of NOL carryforwards for 2009. As a result, our Federal NOL carryforwards are lower than our California NOL 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 our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Beginning balance of unrecognized tax benefits	$ 23,964	$ 10,872	$ 9,834
Decrease for prior period tax positions	(1,653)	—	(174)
Increase for prior period tax positions	—	9,821	791
Increase for current period tax positions	5,054	3,271	421
Ending balance of unrecognized tax benefits	$ 27,365	$ 23,964	$ 10,872

Our unrecognized gross tax benefits presented above would not reduce our annual effective tax rate if recognized because we have recorded a full valuation allowance on our deferred tax assets. We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months. We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2014.

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 is reflected in the Company's estimated annual effective tax rate for 2013.

7. Collaborative Arrangements and Licensing Agreements

Pharmaceutical Alliances and Licensing

AstraZeneca

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$, formerly ISIS-STAT3$_{Rx}$, and ISIS-AR-2.5$_{Rx}$, formerly ISIS-AR$_{Rx}$, for the treatment of cancer and an option to license up to three anti-cancer drugs under a separate research program. Together with AstraZeneca, we are evaluating ISIS-STAT3-2.5$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a clinical study of ISIS-STAT3-2.5$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are conducting a clinical study evaluating ISIS-STAT3-2.5$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$. In June 2013, we and AstraZeneca added a second development candidate, ISIS-AR-2.5$_{Rx}$, to our collaboration. ISIS-AR-2.5$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. AstraZeneca is currently evaluating ISIS-AR-2.5$_{Rx}$ in a Phase 1/2 study in patients with AR-related cancers. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-AR-2.5$_{Rx}$. In addition, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities for such drug.

Under the terms of the agreement, we received $31 million comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013. We recorded revenue of $11.5 million upon receipt of these payments. We are recognizing the remaining $19.5 million into revenue as follows:

- $11.2 million related to the ISIS-AR-2.5$_{Rx}$ program, which we amortized through March 2014;
- $7.6 million related to the option to license three drugs under a separate research program, which we are amortizing through December 2016; and
- $0.7 million related to the ISIS-STAT3-2.5$_{Rx}$ program, which we amortized through February 2015.

In June 2014, we earned a $15 million milestone payment when AstraZeneca initiated a Phase 1 study of ISIS-AR-2.5$_{Rx}$. From inception through February 2015, we have earned $25 million in milestone payments related to the development of ISIS-AR-2.5$_{Rx}$.

In October 2014, we and AstraZeneca amended our agreement for ISIS-STAT3-2.5$_{Rx}$. Under the amended terms of the agreement, we received a $7.5 million milestone payment in November 2014 from AstraZeneca for advancing ISIS-STAT3-2.5$_{Rx}$ in patients with advanced cancers. We recognized into revenue $7.1 million of the $7.5 million milestone payment when we received the payment in November 2014 and we amortized the remaining balance through February 2015. Upon AstraZeneca's initiation of a Phase 2 study, we will earn a $17.5 million milestone payment.

We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive royalties up to the low to mid-teens on any product sales of drugs resulting from this collaboration. If AstraZeneca successfully develops ISIS-STAT3-2.5$_{Rx}$, ISIS-AR-2.5$_{Rx}$, and the three drugs under the research program, we could receive substantive milestone payments of more than $858 million, including up to $238 million for the achievement of development milestones and up to $620 million for the achievement of regulatory milestones. We will earn the next milestone payment of $10 million if we designate a development candidate for a cancer drug under our research program with AstraZeneca.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration. If AstraZeneca exercises its option, it will be responsible for all further global development, regulatory and commercialization activities for such drug. We received a $0.8 million upfront payment, which we are amortizing through December 2016. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.3 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.3 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Our agreement with AstraZeneca will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012 we earned revenue of $27.7 million, $29.1 million and $9.3 million, respectively, from our relationship with AstraZeneca, which represented 13 percent, 20 percent and nine percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2014 and 2013 included deferred revenue of $4.4 million and $9.3 million, respectively, related to our relationship with AstraZeneca.

Biogen Idec

We have established four strategic collaborations with Biogen Idec that broaden and expand our severe and rare disease franchise for neurological disorders.

ISIS-SMN$_{Rx}$

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We are currently conducting a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. In addition, we are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation study in infants with SMA. Patients from both of the Phase 2 studies continue to have access to ISIS-SMN$_{Rx}$ through open-label extension dosing. We are responsible for completing the Phase 2 and Phase 3 trials we are currently conducting. If Biogen Idec exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen Idec has the option to license ISIS-SMN$_{Rx}$. Biogen Idec may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA.

We received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. In 2014, we and Biogen Idec amended our original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. As a result, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by approximately $57 million. Under the terms of the amended agreement, we are eligible to receive up to $327 million in a license fee and payments, including $102.2 million in substantive milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. We will earn the next milestone payment of $9 million if we further advance the Phase 3 study in infants with SMA.

In 2014, we earned an $18 million milestone payment when we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and we earned a $27 million milestone payment when we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. From inception through February 2015, we have earned $71.3 million in payments for advancing ISIS-SMN$_{Rx}$. We are amortizing a portion of those payments as follows:

- $3.8 million related to the Phase 2 studies in children and infants with SMA, which we amortized through July 2014; and
- $7.5 million related to an open-label extension study in children with SMA, which we are amortizing through March 2015.

ISIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen Idec entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, ISIS-DMPK-2.5$_{Rx}$, formerly ISIS-DMPK-2$_{Rx}$, targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the first Phase 2 trial. If Biogen Idec exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments, including up to $59 million in development milestone payments and $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of the drug. From inception through February 2015, we have earned $24 million in milestone payments associated with the clinical development of ISIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $35 million if we initiate a Phase 2 study for ISIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen Idec has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. If Biogen Idec exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We are eligible to receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials. We are also eligible to receive up to $130 million in milestone payments per program if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of drugs resulting from each of the three programs. In February 2015, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study of ISIS-BIIB4$_{Rx}$, a drug for an undisclosed target designed to treat a neurodegenerative disease. We will earn the next milestone payment of up to $14 million if we initiate a Phase 1 study for ISIS-BIIB4$_{Rx}$.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration agreement, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. If Biogen Idec exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive single-digit royalties on any product sales of drugs using non-antisense modalities developed under this collaboration. Through February 2015, we have earned $25 million in milestone payments related to advancing three different targets under this collaboration. We will earn the next milestone payment of up to $10 million if we choose another target to advance under this collaboration.

Each of our agreements with Biogen Idec will continue until the earlier of the date all of Biogen Idec's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen Idec exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen Idec may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen Idec may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen Idec may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen Idec may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012, we earned revenue of $123.2 million, $37.0 million and $8.5 million, respectively, from our relationship with Biogen Idec, which represented 58 percent, 25 percent and eight percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2014 and 2013 included deferred revenue of $118.1 million and $145.1 million, respectively, related to our relationship with Biogen Idec.

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. There are monthly limits on the number of shares of our stock that Genzyme can sell. From inception through February 2015, we have earned $50 million in milestone payments for advancing KYNAMRO in development. 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 equal to or greater than $250 million in a calendar year.

Under our alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. 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 are sharing development expenses equally until 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.

During 2013 and 2012, we earned revenue of $32.5 million, and $67.6 million, respectively, from our relationship with Genzyme, which represented 22 percent and 66 percent, respectively, of our total revenue for those years. During 2014, we did not earn any revenue from our relationship with Genzyme.

GSK

In March 2010, we entered into a strategic alliance with GSK using 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. Our strategic alliance currently includes five drugs in development. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when we and GSK expanded the collaboration.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. From inception through February 2015, we have received $45 million, primarily in milestone payments, from GSK related to the development of ISIS-TTR_{Rx}. We are also eligible to earn an additional $25 million in pre-licensing milestone payments associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} receive marketing approval and meet pre-agreed sales targets.

In addition to ISIS-TTR_{Rx}, we have four drugs in development. We are developing ISIS-HBV_{Rx}, an antisense drug designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection. We are also developing ISIS-GSK4-L_{Rx} and ISIS-RHO-2.5_{Rx}, formerly ISIS-$GSK5_{Rx}$, which are antisense drugs we designed to treat ocular diseases. In addition, we recently advanced a drug to treat an undisclosed target, ISIS-GSK6-L_{Rx}, into development.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.2 billion, including up to $146.5 million for the achievement of development milestones, up to $483.5 million for the achievement of regulatory milestones and up to $428 million for the achievement of commercialization milestones. We will earn the next $15 million milestone payment if we further advance ISIS-TTR_{Rx}. In addition, we are eligible to receive royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the ISIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the ISIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012, we earned revenue of $37.3 million, $35.3 million and $8.2 million, respectively, from our relationship with GSK, which represented 17 percent, 24 percent and eight percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2014 and 2013 included deferred revenue of $10.0 million and $11.5 million, respectively, related to our relationship with GSK.

Janssen Biotech, Inc., a pharmaceutical company of Johnson & Johnson

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal, or GI, tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in payments, made up of a $30 million payment we received in December 2014 and a $5 million payment we received in February 2015. We are amortizing these payments through December 2018. We are eligible to receive nearly $800 million in substantive milestone payments and license fees for these programs, including up to $175 million for the achievement of development milestones, up to $420 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the near teens on any product sales of drugs resulting from this collaboration. We will earn the next milestone payment of $5 million if Janssen chooses another target to advance under this collaboration.

Our agreement with Janssen will continue until the earlier of the date that all of Janssen's options to obtain the exclusive licenses under the agreement expire unexercised or, if Janssen exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Janssen may terminate the agreement or any program at any time by providing written notice to us; and
- Either we or Janssen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2014, 2013 and 2012 we did not earn any revenue from our relationship with Janssen. Our balance sheet at December 31, 2014 included deferred revenue of $30 million related to our relationship with Janssen.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestone payments. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us;
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent; and
- Either we or Roche may terminate the brain shuttle program if at least one development candidate is not designated under such program by a mutually agreed deadline.

During 2014 and 2013, we earned revenue of $8.7 million and $5.1 million, respectively from our relationship with Roche. Our balance sheet at December 31, 2014 and 2013 included deferred revenue of $17 million and $25 million, respectively related to our relationship with Roche.

Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively licensed 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. Plazomicin 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 earned $7 million in milestone payments from Achaogen, including a $4 million milestone payment we earned in September 2014 when Achaogen initiated a Phase 3 study of plazomicin in patients with serious multi-drug resistant, gram-negative bacterial infections. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $42.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $7.5 million if Achaogen obtains regulatory approval for plazomicin in a major market. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

During 2014 we earned $4 million in revenue from our relationship with Achaogen. During 2013 and 2012, we did not earn any revenue from our relationship with Achaogen. During 2014, we sold all of the Achaogen stock we owned resulting in net proceeds of $1.3 million.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference 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 from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include 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. In December 2014, we earned a $0.4 million milestone payment from Alnylam for the initiation of a Phase 1 study. We will earn the next milestone payment of $0.4 million if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We also have the potential to earn a portion of payments that Alnylam receives from licenses of our technology it grants to its partners plus royalties. Through February 2015, we have earned a total of $50.8 million from Alnylam resulting from licenses of our technology Alnylam has granted to its partners, including $9.5 million we earned in 2014. 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 single-stranded antisense therapeutics, or 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 up to $3.4 million in milestone payments for specified development and regulatory events plus royalties. To date, we do 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 January 2015, we and Alnylam entered into a new alliance in which we formed an intellectual property cross-license with reciprocal economic terms on four therapeutic targets. Under the terms of the agreement, we and Alnylam each obtained exclusive license rights to two therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA-targeting mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets, Factor XI and apolipoprotein (a). In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA-targeting mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets, antithrombin and aminolevulinic acid synthase-1. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics.

During 2014, 2013 and 2012, we earned revenue from our relationship with Alnylam totaling $9.9 million, $1.5 million and $2.7 million, respectively.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is developing ATL1102 for the treatment of multiple sclerosis. In addition, ATL is currently developing ATL1103 for growth and sight disorders. 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, 2014 and 2013, we owned less than 10 percent of ATL's equity. During 2014, 2013 and 2012, we did not earn any revenue 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.

Under the agreement, we could receive milestone substantive payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $0.6 million if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for patients with inflammatory bowel disease, or IBD, for which we receive royalties.

In 2010 and 2013, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we agreed to receive equity for the royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of value from the equity is uncertain. At December 31, 2014 and 2013, we owned approximately 12 percent of Atlantic Pharmaceuticals' equity. We earned $0.7 million related to royalties and sales of drug substance in 2013. Because the payments were made in equity, we did not record any revenue. During 2014 and 2012, our revenue was negligible 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 $6.5 million in contingent payments from Pfizer 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, if 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 also eligible to receive royalties on any product sales of EXC 001.

At December 31, 2014, we owned no equity in Excaliard. During 2013 and 2012, we received $0.8 million and $1.3 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard and for advancing of EXC 001, which we recorded as investment gains. We did not earn any revenue during 2014, 2013 and 2012 from our relationship with Excaliard.

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

Custirsen, formerly OGX-011

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, 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 core antisense technology patents we licensed to OncoGenex are U.S. Patent number 7,919,472 having an expiration date of 2026, its foreign equivalents granted in Australia and Canada, and its foreign equivalent pending under the European Patent Convention. 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. OncoGenex recently announced that it executed an initial agreement with Teva to regain rights to custirsen.

OGX-225

In August 2003, we and OncoGenex entered into a second and separate agreement for the development of an 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 $0.8 million 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, 2014, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $0.5 million if OncoGenex initiates a Phase 2 study for OGX-225.

Apatorsen, formerly OGX-427

In January 2005, we entered into a third and separate agreement with OncoGenex to allow for the development of an additional antisense anti-cancer drug, apatorsen. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex will pay us 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. We will earn the next milestone payment of $1.3 million if OncoGenex initiates a Phase 3 study for apatorsen.

During 2014, 2013 and 2012, 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. 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, atherosclerosis and viral infections, such as Hepatitis C virus, and currently has two drugs in development. Regulus is developing RG-101, an anti-miR that targets microRNA-122, for the treatment of HCV infection. Regulus is also developing RG-012, an anti-miR that targets microRNA-21, for the treatment of Alport Syndrome. We are eligible to receive royalties on any future product sales of both of these drugs.

Regulus has strategic partnerships with Sanofi, Biogen Idec and AstraZeneca. We benefit from Regulus' strategic partnerships because we have the potential to receive a portion of upfront payments, future milestone payments, and/or royalty payments. For example, under Regulus' strategic partnership with Sanofi, and as a result of our agreement with Regulus, we received 7.5 percent, or $1.9 million, of the $25 million upfront payment.

During 2014, 2013 and 2012, we did not earn any revenue from our relationship with Regulus. During 2014, we sold a portion of our Regulus stock, resulting in a $19.9 million gain and cash of $22.9 million. As of December 31, 2014, we remain a significant shareholder with approximately 5.5 million shares, approximately 11 percent of Regulus' equity, with a net carrying value of $81.9 million.

External Project Funding

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. In 2013, we made two payments to CHDI totaling $3 million associated with the progression of our Huntington's disease program, which we recorded as research and development expense. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI. During 2013 and 2012, we earned revenue of $0.4 million and $2.0 million, respectively, from our relationship with CHDI. During 2014, 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 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.

Intellectual Property Sale and Licensing Agreements

Sales of Intellectual Property

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, we are eligible to receive earn out payments from AMI equal to a percentage of Ibis' revenue related to sales of Ibis systems, which AMI launched in 2014 as IRIDICA, including instruments, assay kits and successor products. Once cumulative net sales reach $140 million, and through December 31, 2025, we are eligible to earn out payments in any year that net sales exceed $50 million for the applicable year. 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 2014, 2013 and 2012, we did not earn any revenue from our relationship with AMI.

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 small interfering RNA, or 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.

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 a milestone payment to the University of Massachusetts of $0.3 million for the achievement of a key regulatory milestone. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive in consideration for sublicensing its technology, and a royalty on sales of ISIS-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 a milestone payment of $0.5 million to the Cold Spring Harbor Laboratory for the achievement of a key regulatory milestone. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue and post licensing milestone payments up to $11.3 million we receive in consideration for sublicensing the Cold Spring Harbor Laboratory's technology and a royalty on sales of ISIS-SMN$_{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:

	2014	2013	2012
Partner A	58%	25%	8%
Partner B	17%	24%	8%
Partner C	13%	20%	9%
Partner D	0%	22%	66%

Contract receivables from three significant partners comprised approximately 99 percent of our contract receivables at December 31, 2014 and contract receivables from three significant partners comprised approximately 91 percent of our contract receivables at December 31, 2013.

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 ($17,500 and $23,000 in 2014 for employees under 50 years old and employees 50 years old or over, respectively). We made approximately $1.0 million, $0.6 million and $0.5 million in matching contributions for the years ended December 31, 2014, 2013 and 2012, respectively.

10. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates. We do not believe, relative to our current legal proceedings, that a loss is both probable and estimable. As such, as of December 31, 2014, we do not have a liability related to any of our current legal proceedings, including the following matters.

Santaris Litigation

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). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion.

In March 2014, Santaris filed a motion asking the court to decide that Santaris' alleged infringing sales of Isis' patented methods are not actionable as a matter of law. In June 2014, the court granted Santaris' motion and dismissed our allegations to the extent the allegations are based on Santaris' sale or offer for sale of such method claims; and that we did not plead sufficient facts to establish that Santaris entering into its agreement with Enzon constituted the sale or offer for sale of the compounds claimed in U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739. The rest of the case is proceeding, and on October 17, 2014, we filed an amended complaint to plead additional facts and assert Santaris infringed U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739 through Santaris' agreement with Enzon.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Isis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. we and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents will infringe those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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, 2014 and 2013 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2014 Quarters				
Revenue	$ 28,161	$ 57,076	$ 44,063	$ 84,861
Operating expenses	57,828	63,726	65,556	74,781
Income (loss) from operations	(29,667)	(6,650)	(21,493)	10,080
Net income (loss)	$ (31,280)	$ (12,081)	$ (26,676)	$ 31,053
Basic net income (loss) per share (1)	$ (0.27)	$ (0.10)	$ (0.23)	$ 0.26
Diluted net income (loss) per share (1) (2)	$ (0.27)	$ (0.10)	$ (0.23)	$ 0.25

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2013 Quarters				
Revenue	$ 43,360	$ 38,092	$ 23,585	$ 42,248
Operating expenses	41,735	46,020	49,090	62,106
Income (loss) from operations	1,625	(7,928)	(25,505)	(19,858)
Net loss	$ (1,672)	$ (10,126)	$ (24,570)	$ (24,276)
Basic and diluted net loss per share (1)	$ (0.02)	$ (0.09)	$ (0.21)	$ (0.21)

(1) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for the year.

(2) For the fourth quarter of 2014, we had net income and as a result we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. Diluted common equivalent shares for the three months ended December 31, 2014 consisted of:

- 4.2 million shares issuable upon exercise of stock options
- 0.4 million shares issuable upon restricted stock award issuance; and
- 0.009 million shares issuable related to our ESPP.

The calculation excludes the 1 percent and 2¾ percent convertible senior notes because the effect on diluted earnings per share would be anti-dilutive.

EXHIBIT 10.59

December 15, 2014

B. Lynne Parshall, Chief Operating Officer
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Fax: (760) 918-3592

Re: Amendment #1 to the SMA Agreement ("*Amendment #1*")

Dear Lynne:

Reference is hereby made to that certain Development, Option and License Agreement by and between Isis Pharmaceuticals, Inc. ("***Isis***") and Biogen Idec International Holding Ltd ("***Biogen Idec***") dated January 3, 2012, as supplemented and/or amended to date (the "***SMA Agreement***"). Any capitalized terms not defined herein shall have the meaning set forth in the SMA Agreement.

Biogen Idec and Isis hereby acknowledge and agree that the SMA Agreement is hereby amended as follows:

1. The definition of "Additional Development Plan Costs" in Appendix 1 of the SMA Agreement is hereby amended, superseded and replaced in its entirety to read as follows:

"***Additional Development Plan Costs***" means [***].

For clarity, the amended definition of Additional Development Plan Costs shall only apply with respect to Additional Development Plan Costs that are invoiced by Isis pursuant to Section 1.4.2(a) of the SMA Agreement following the date of this Amendment #1, and does not apply to any invoices for costs prior to the date of this Amendment #1 or that have been agreed to pursuant to the letter agreements between the parties dated January 27, 2014, August 13, 2014, October 7, 2014 and October 13, 2014.

2. The following definitions are hereby added to Appendix 1 of the SMA Agreement:

"***CS3A Study***" means the ISIS 396443-CS3A Clinical Study described in the ISIS-SMN_{Rx} Development Plan.

"***CS3B Study***" means the ISIS 396443-CS3B Clinical Study described in the ISIS-SMN_{Rx} Development Plan.

"***CS5 Study***" means the ISIS 396443-CS5 Clinical Study described in the ISIS-SMN_{Rx} Development Plan.

"***CS12 Study***" means the ISIS 396443-CS12 Clinical Study described in the ISIS-SMN_{Rx} Development Plan.

"***CS7 Study***" means the ISIS 396443-CS7 Clinical Study described in the ISIS-SMN_{Rx} Development Plan.

"***Isis/Biogen Idec Additional Agreements***" means the (i) DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012, (ii) Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated December 10, 2012 and (iii) the Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated September 5, 2013, in each case, as amended and/or restated from time to time.

3. The definition of "PoC Trial" in Appendix 1 of the SMA Agreement is hereby amended, superseded and replaced in its entirety to read as follows:

"***PoC Trial***" means (A) either (i) the CS3B Study, if the CS3B Study [***] set forth in the protocol for the CS3B Study, or (ii) the CS4 Study, if the CS4 Study [***] set forth in the protocol for the CS4 Study, (B) completion of both the CS3B Study and the CS4 Study, irrespective of whether any such Clinical Studies [***] as set forth in the protocols for such Clinical Studies, or (C) the CS3A Study if Biogen Idec notifies Isis that [***].

4. The following revisions are made to the license fee payments and timing under the SMA Agreement, in the event wherein a PoC Trial Completion Notice is delivered either for [***] or [***]:

a. ***Where the [***] Study is the First PoC Trial to Achieve [***]***. Notwithstanding anything to the contrary in the SMA Agreement, in the event that pursuant to Section 3.1.2 of the SMA Agreement Isis delivers a complete PoC Trial Completion Notice to Biogen Idec with respect to the [***] Study before the completion of the [***] Study, then:

(i) the Option Deadline (the "[***] Option Deadline") shall be as set forth in Section 3.1.3 of the SMA Agreement; and

(ii) the license fee set forth in Section 6.3 of the SMA Agreement shall be $[***] (the "[***] License Fee").

b. ***Where the [***] Study is the First PoC Trial to Achieve [***]***. Notwithstanding anything to the contrary in the SMA Agreement, in the event that pursuant to Section 3.1.2 of the SMA Agreement Isis delivers a complete PoC Trial Completion Notice to Biogen Idec with respect to the [***] Study before the completion of the [***] Study, then:

(i) Biogen Idec will pay Isis $[***] (the "[***] ***Clinical Success Fee***") within [***] days after receipt of such complete PoC Trial Completion Notice;

(ii) the license fee set forth in Section 6.3 of the SMA Agreement shall be $[***] (the "[***] License Fee"); and

(iii) the Option Deadline (the "[***] Option Deadline") shall be the earlier of (x) [***] days following the date upon which [***], or (y) [***] days following Biogen Idec's receipt of [***]; *provided* if at the time Biogen Idec receives such [***], (A) the [***] Study [***] set forth in the protocol for the [***] Study, and (B) Isis has [***], then the [***] Option Deadline will be [***] days following the earlier of (I) the [***], or (II) the [***].

Together with Biogen Idec's written notice to Isis that it is exercising the Option and payment to Isis of the [***] License Fee by such [***] Option Deadline, the Option shall be deemed exercised. If Biogen Idec does not provide Isis a written notice that Biogen Idec is exercising the Option and pay Isis the [***] License Fee by the [***] Option Deadline, then the SMA Agreement will expire in accordance with Section 10.1.3 of the SMA Agreement.

c. If the total amount of the [***] License Fee or the total sum of the [***] License Fee and the [***] Clinical Success Fee, as applicable, paid to Isis by Biogen Idec under this Amendment #1 equals $[***], an incremental additional royalty of [***]% shall be applied to the portion of Annual Worldwide Net Sales equal to or greater than $[***] (subject to any applicable royalty reductions set forth in Section 6.6.2 of the SMA Agreement) until Isis receives $[***] from this additional royalty. Once Isis has received such additional $[***] more in royalties, the royalty rates will revert back to the original royalty rates for the portion of Annual Worldwide Net Sales equal to or greater than $[***] in Section 6.6.1 of the SMA Agreement, subject to any applicable royalty rate reductions set forth in Section 6.6.2 of the SMA Agreement.

5. If the decision is made to file an NDA and/or MAA based on data from the [***] Study, the [***] Interim Data, and/or the [***] Interim Data, the following provisions will apply:

a. ***Where either an NDA and/or an MAA is Submitted Based on the [***].*** Notwithstanding anything to the contrary in the SMA Agreement, Biogen Idec may [***] request in writing that Isis submit an NDA to the FDA and/or an MAA to the EMA based upon the data from the [***] Study. Should Biogen Idec notify Isis in writing that Isis should submit an NDA to the FDA and/or an MAA to the EMA based upon the data from such [***] Study, then, subject to paragraphs 6 and 7 below, Isis shall submit such NDA and/or MAA and then:

(i) The Option Deadline (the "[***] Option Deadline") shall be the earlier of (x) [***] days following the earliest date upon which [***], as applicable, or (y) [***] days following Biogen Idec's receipt of [***]; and

(ii) the license fee set forth in Section 6.3 of the SMA Agreement will be $[***] (the "[***] License Fee") and will be due by such [***] Option Deadline.

For the avoidance of doubt, the [***] Study shall not be deemed [***] unless Biogen Idec notifies Isis that Biogen Idec wants Isis to submit either or both an NDA to the FDA and/or an MAA to the EMA based upon the data from the [***] Study. [***].

b. ***Where Biogen Idec Submits either an NDA and/or an MAA Based on the [***] Interim Data***. Notwithstanding anything to the contrary in the SMA Agreement, in the event that Isis delivers interim data to Biogen Idec with respect to the [***] Study ("[***] ***Interim Data***"), Biogen Idec, at its sole discretion, shall have [***] days in which to notify Isis that it will submit an NDA to the FDA and/or an MAA to the EMA based upon such [***] Interim Data (the "[***] ***Interim Data Filing Notice***"). If Biogen Idec timely provides Isis a [***] Interim Data Filing Notice, then the Option shall be deemed exercised, and Biogen Idec will pay Isis the license fee of $[***] at the same time Biogen Idec delivers the [***] Interim Data Filing Notice.

c. ***Where either an NDA and/or an MAA is Submitted Based on the [***] Interim Data***. Notwithstanding anything to the contrary in the SMA Agreement, in the event that Isis delivers interim data to Biogen Idec with respect to the [***] Study ("[***] ***Interim Data***"), Biogen Idec, at its sole discretion, shall have [***] days in which to notify Isis in writing whether or not Biogen Idec wants Isis to submit an NDA to the FDA and/or an MAA to the EMA based upon the [***] Interim Data. If, within such [***] day period, Biogen Idec notifies Isis in writing that it wants Isis to submit an NDA to the FDA and/or an MAA to the EMA based upon the [***] Interim Data (the "[***] ***Interim Data Filing Notice***"), then:

(i) Biogen Idec will pay Isis $[***] (the "[***] ***Interim Filing Fee***") at the same time Biogen Idec delivers the [***] Interim Data Filing Notice;

(ii) the license fee set forth in Section 6.3 of the SMA Agreement shall be $[***] (the "[***] Interim License Fee"); and

(iii) the Option Deadline (the "[***] Interim Option Deadline") shall be the earlier of (x) [***] days following the earliest date upon which [***], as applicable, (y) [***] days following Biogen Idec's receipt of a complete PoC Trial Completion Notice for the [***], or (z) 60 days following Biogen Idec's receipt of [***] for both the [***] and the [***].

Together with Biogen Idec's written notice to Isis that it is exercising the Option and payment to Isis of the [***] Interim License Fee by the [***] Interim Option Deadline, the Option shall be deemed exercised. If Biogen Idec does not provide Isis a written notice that Biogen Idec is exercising the Option and pay the [***] Interim License by the [***] Interim Option Deadline, then the SMA Agreement will expire in accordance with Section 10.1.3 of the SMA Agreement.

6. In all cases where Biogen Idec has requested Isis to submit (or following Option exercise where Biogen Idec chooses to submit) an NDA and/or MAA for filing under this Amendment #1, Biogen Idec shall be responsible for [***] and the IND-holder at the time of such filing (either Biogen Idec or Isis) shall be responsible for submitting such NDA to the FDA and/or such MAA to the EMA. If Isis is the IND-holder at the time of filing such NDA or MAA, Isis will [***], but Biogen Idec may [***]. If Biogen Idec is the IND-holder at the time of filing such NDA or MAA, Biogen Idec will [***]. Upon Biogen Idec's request, Isis will assist Biogen Idec in [***], and Biogen Idec [***] incurred by Isis in providing such assistance; *provided, however*, that Isis shall be responsible for [***].

Subject to the terms and conditions of this Amendment #1, Isis will not assert any of the Licensed Technology against Biogen Idec or its successors or assigns solely based on Biogen Idec preparing an NDA or MAA in accordance with this Amendment #1.

7. If Biogen Idec requests Isis submit an NDA or MAA based upon the data from the [***] Study, delivers a [***] Interim Data Filing Notice or delivers a [***] Interim Data Filing Notice, Isis shall as soon as practicable (but no later than [***] days after such request or delivery) transfer all regulatory documentation (including drafts), and the relevant Isis Know-How (including Manufacturing and Analytical Know-How) to Biogen Idec pursuant to Section 4.5 of the SMA Agreement. In all cases where Biogen Idec exercises the Option, as soon as practicable (but no later than [***] days after Biogen Idec exercises its Option under this Amendment #1) transfer and assign the regulatory filings, including the IND to Biogen Idec pursuant to Section 4.5 of the SMA Agreement.

8. If Biogen Idec receives a [***] based upon [***], the following provisions shall apply:

a. Biogen Idec shall be the sole and exclusive owner of such [***].

b. In the event that Biogen Idec sells or otherwise transfers such [***] to a Third Party, then any consideration received by Biogen Idec in exchange for such [***] shall be [***] for purposes of Article 6 of the SMA Agreement. Biogen Idec and Isis will mutually agree on the [***] for purposes of this paragraph 8(b).

c. Biogen Idec shall determine, in its sole discretion, whether to [***] to a [***] or to [***] to a Third Party. If Biogen Idec determines to [***], then Biogen Idec shall [***].

9. Biogen Idec hereby agrees to use Commercially Reasonable Efforts to undertake the [***] Study and the [***] Study.

If you accept the terms and conditions set forth in this Amendment #1, please so indicate by executing a copy of this letter and returning it to Biogen Idec. Upon execution by both Isis and Biogen Idec, this Amendment #1 shall be considered part of the SMA Agreement (including Sections 12.11 and 12.17 of the SMA Agreement) but, except as expressly provided above, shall not be deemed to modify or amend any provision of the SMA Agreement. All other provisions of the SMA Agreement will remain in full force and effect.

This Amendment #1 may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from electronic transmission, store and printing of copies of this Amendment #1 from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[Signature page follows]

Sincerely,

/s/ Richard Brudnick

Richard Brudnick
Senior Vice President, Corporate Development
BIOGEN IDEC MA INC.

/s/ Frederick Lawson

Frederick Lawson, Director
BIOGEN IDEC INTERNATIONAL GMBH

AGREED AND CONFIRMED ON BEHALF OF ISIS PHARMACEUTICALS, INC.:

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer

Date:

Cc: Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: (760) 268-4922

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

EXHIBIT 10.60

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

JANSSEN BIOTECH INC.

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

This RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 22nd day of December, 2014 (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 **JANSSEN BIOTECH INC.**, a Pennsylvania company, with principal offices located at 800/850 Ridgeview Road, Horsham, PA 19044 ("**JBI**") JBI 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, JBI has expertise in developing and commercializing human therapeutics, and JBI is interested in developing and commercializing antisense therapeutics for initially up to three gene targets implicated in Autoimmune Disease (with the right to add a fourth target by paying an additional fee);

WHEREAS, the Parties desire to enter into a collaborative enterprise pursuant to which (i) the Parties will conduct activities directed toward researching, discovering and developing therapeutic antisense oligonucleotides designed to bind and modulate the RNA of each collaboration target, (ii) Isis will endeavor to identify a development candidate for each collaboration target, and (iii) for each collaboration target for which Isis identifies a development candidate, JBI will have an exclusive 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 COLLABORATION

1.1 **Collaboration Overview**. The intent of the Collaboration is: (i) for the Parties to conduct a Drug Discovery Program, including formulation activities, for each of the Collaboration Targets and to share their respective expertise to advance the goals set out in the Drug Discovery Plan for each such Drug Discovery Program; (ii) for Isis to generate at least one Development Candidate under each Drug Discovery Program; (iii) for JBI to have an Option to obtain an exclusive license to Develop and Commercialize Products under each Drug Discovery Program in the Field; and (iv) if JBI exercises the Option for a Drug Discovery Program, the Parties will advance the Development Candidate through IND-Enabling Toxicology Studies, and thereafter JBI will continue to Develop and Commercialize the applicable Development Candidate. 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, 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 Targets.

1.2.1 **Maximum Number; Initial Collaboration Target**. The maximum number of Collaboration Targets will be three, subject to Section 1.2.2. The Parties agree that the first Collaboration Target is [***]. JBI will designate the second Collaboration Target within [***] of the Effective Date, and designate the third Collaboration Target within [***] of the Effective Date (each, a ***"Target Nomination Period"***), in each case in accordance with the mechanism set forth in Section 1.2.3 below.

1.2.2 **Optional Fourth Collaboration Target**. JBI will have the right, exercisable within [***] after the Effective Date, to designate a fourth Collaboration Target (*i.e.*, to increase the maximum number of Collaboration Targets by one) in accordance with the mechanism set forth in Section 1.2.3 below upon delivery of written notice thereof to Isis and payment to Isis of the $[***] fee pursuant to Section 6.2, *provided* if JBI exercises such right, JBI must (i) designate such fourth Collaboration Target within [***] after the Effective Date and (ii) JBI may extend the Drug Discovery Term, if necessary, for the time required to execute under a corresponding Drug Discovery Plan for such fourth Collaboration Target under Section 1.5.2. Any [***] shall only become due if the [***], and any [***] shall be [***], and such [***] within [***] days of [***] following the date such Drug Discovery Plan is approved.

1.2.3 **Collaboration Target Designation Mechanism**. At any time during the applicable Target Nomination Period, JBI may propose a gene target implicated in Autoimmune Disease of the gastro-intestinal tract for designation as a Collaboration Target by providing written notice of such gene target to Isis. Isis may reject a gene target proposed by JBI if, at the time of such proposal: (i) Isis believes in good faith that [***] for such target; (ii) Isis does not have the [***]; (iii) granting a license to such target would [***] to a Third Party and JBI does not [***]; (iv) [***]; (v) the proposed target is the subject of [***] for which Isis in good faith expects to [***] (although Isis will negotiate in good faith terms for JBI to gain access such a program); or (vi) the target is associated with [***] (each of (i) through (vi), a ***"Dispositive Rejection Condition"***). If a Dispositive Rejection Condition for the gene target proposed by JBI for designation as a Collaboration Target exists, Isis may reject the proposed gene target by providing a written notice to JBI by the [***] day following Isis' receipt of JBI's request to designate such gene target as a Collaboration Target, in which event JBI may propose a different gene target for designation as a Collaboration Target using the process described above in this Section 1.2.3.

1.2.4 **Collaboration Target Designation**. A gene target proposed by JBI for designation as a Collaboration Target in accordance with Section 1.2.3 above will become a "Collaboration Target" if (i) Isis provides JBI a written notice accepting such gene target as a Collaboration Target or (ii) by the [***] day following Isis' receipt of JBI's request to designate such gene target as a Collaboration Target, Isis has not delivered a written notice to JBI rejecting such gene target based on a Dispositive Rejection Condition.

1.2.5 **Substitution of Gene Targets.** At any time prior to completion of [***] activities for a Collaboration Target, JBI may propose, in writing, a substitute gene target to replace such Collaboration Target subject to the following conditions:

i) JBI may propose up to [***] ([***]) substitute gene targets, unless JBI designates a Fourth Collaboration Target whereby, in which case JBI may then propose up to [***] ([***]) substitute gene targets;

ii) JBI shall pay the Substitution Fee for each proposed substitute gene target within [***] ([***]) days of the date the substitute gene target becomes a Collaboration Target under Section 1.2.4; and

iii) The designation mechanism of Section 1.2.3 shall apply for proposed substitute gene targets.

Any gene target substituted out under this Section 1.2.5 will no longer be a Collaboration Target.

1.3 **Drug Discovery and Development Responsibilities**.

1.3.1 **Drug Discovery Programs**. Subject to the terms and conditions of this Agreement, during the Drug Discovery Term, the Parties will jointly conduct collaborative research projects directed to the research, discovery and pre-clinical development of ASOs designed to bind to and modulate the RNA of each Collaboration Target (subject to the applicable maximum number of Collaboration Targets under Section 1.2) (each, a ***"Drug Discovery Program"***).

1.3.2 **Drug Discovery Plans and Development Plans**.

(a) For each Drug Discovery Program, the Parties, via the JRC, will: (i) promptly (but no later than [***] days) following the designation of such Collaboration Target, approve a written plan describing the discovery, research, and optimization activities to be conducted by each Party to achieve [***] status and to identify a Development Candidate, plus any related research activities to support such activities; and (ii) from time to time thereafter, consider and approve appropriate amendments and modifications to such plan (each such plan, as so amended, a ***"Drug Discovery Plan"***). By separate agreement the Parties have agreed upon the initial Drug Discovery Plan for the Drug Discovery Program directed to [***]. Upon JRC approval of the Drug Discovery Plan for any other Collaboration Target, or upon JRC approval of any amendment or modification to any Drug Discovery Plan, the JRC will attach such Drug Discovery Plan, or such amendment or modification (as applicable), to the minutes of the JRC meeting at which the same is approved.

(b) For each Drug Discovery Program with respect to which JBI exercises the Option, JBI will share with Isis, via the JRC (or directly with Isis if the JRC has dissolved) (i) promptly (but no later than [***] days) following such Option exercise, a written plan describing the proposed Development activities to be conducted by JBI with respect to the applicable Development Candidate; and (ii) from time to time thereafter consider and make appropriate amendments and modifications to such plan (each such plan, as so amended, a ***"Development Plan"***). The Parties, at their respective expense, shall meet and confer regarding the activities proposed under the Development Plan and, to the extent there are activities required of Isis under the Development Plan, shall agree on such activities within a reasonable amount of time but not to exceed [***] days following presentation of the Development Plan to the JRC. The JRC will attach such Development Plan or any subsequent amendments or modifications thereto (as applicable) to the minutes of the JRC meeting at which the same is agreed and approved. Each Development Plan will include a description of the pre-clinical studies, and clinical studies (including study designs) to support the further Development of such Development Candidate up to completion of PoC, including [***]. If the Parties agree Isis will conduct any activities to support the further Development of the Development Candidate, the Development Plan will include the specific activities to be performed by Isis and [***] and [***] for completion of such activities. JBI will continue to develop and refine each Development Plan as needed and will submit it to the JRC (or the Parties if the JRC has dissolved) for review and comment at least [***]. When updating each Development Plan, JBI will [***].

1.3.3 **Allocation of Drug Discovery and Development Responsibilities**. Each Drug Discovery Plan and Drug Development Plan will specify the Party(ies) responsible for performing each activity thereunder, and each Party will use Commercially Reasonable Efforts to complete such activities; *provided, however,* that unless otherwise mutually agreed by the Parties in writing each Party will use Commercially Reasonable Efforts to complete the following at each respective company's expense unless otherwise indicated:

(a) Isis will be responsible for [***] under each Drug Discovery Plan;

(b) Except as set forth in Sections (c), (d) and (f) of this Section 1.3.3, Isis will be responsible for [***] and [***], in each case to the extent stated to be conducted by Isis in the applicable Drug Discovery Plan;

(c) JBI will be responsible for conducting the (i) [***], and (ii) the [***] including [***], in each case to achieve [***] status and produce the Development Candidate Data Package;

(d) JBI will be responsible for conducting the [***], in each case to achieve [***] status, produce the Development Candidate Data Package, and to support the further Development and Commercialization of Products. Isis will provide [***] if requested by JBI and JBI will pay Isis for such support at [***] and shall invoice JBI in accordance with Section 6.10;

(e) During the Research Term Isis will (i) [***] and (ii) [***], in each case to the extent stated to be conducted by Isis in the applicable Drug Discovery Plan;

(f) JBI will be responsible for conducting [***], including [***]; and

(g) JBI will be responsible for conducting [***] activities for each Development Candidate, including conducting [***], *except* Isis will be responsible for conducting the [***] of the Development Candidate for the first Drug Discovery Program with respect to which JBI exercises the Option (the "***First Development Candidate***") as specified in the applicable Development Plan.

1.3.4 **Conduct of Drug Discovery and Development Plan Activities**. Each Party will perform the activities for which it is responsible under each Drug Discovery Plan and each Development Plan in good scientific manner and in compliance with, as applicable, GLP, GCP and/or GMP, and all Applicable Laws.

1.3.5 **Disclosure of Results**. At least [***] Business Days prior to each regularly scheduled meeting of the JRC, each Party will provide to the JRC a written report (which may take the form of PowerPoint slides) for each Drug Discovery Program (i) describing the Drug Discovery Program activities performed by such Party since the date of the preceding written report delivered by such Party for such Drug Discovery Program and the status of each such activity as of the date of such report and (ii) summarizing the data and results of the Drug Discovery Program activities performed by such Party under the applicable Plan.

1.3.6 **Development Candidate; Supplemental Information**. Isis will notify JBI promptly after designating a Development Candidate and, together with such notice, Isis will provide JBI with the applicable Development Candidate Data Package. During the [***] period beginning on Isis' delivery of the Development Candidate Data Package to JBI, JBI may request in writing additional data or information regarding the Development Candidate of a type that is consistent with the information JBI examines when selecting JBI's own development candidates for similar programs and that JBI in good faith determines is reasonably necessary to inform JBI's decision of whether to exercise the Option for such Drug Discovery Program (the "***Supplemental Information***"); *provided, however,* that: (i) unless Isis possesses and can reasonably provide the requested data or information, JBI will be solely responsible for conducting or having conducted by Isis ([***]) the work necessary to generate the requested Supplemental Information and for all agreed upon fees and costs incurred by it or for its account in the performance of such work; (ii) Isis will not be required to conduct any such work unless Isis and JBI agree to a plan for such work and JBI agrees to pay for such work at [***] and for both (i) and (ii) shall invoice JBI in accordance with Section 6.10.

1.3.7 **Records and Quality.** Isis will maintain complete and accurate records of all work Isis conducts in the performance of a Drug Discovery Plan and Development Plan and all results, data, inventions and developments made in the performance of such work. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Upon reasonable prior written notice, Isis will provide JBI the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of JBI's rights and obligations under this Agreement or for JBI's reasonable quality control purposes. Isis will cooperate in good faith with respect to the conduct of any inspections by any Regulatory Authority of an Isis site or a contractor's site and facilities if such inspection concerns work being performed under a Drug Discovery Plan or Development Plan. [***]. In the event that during an inspection of the Isis facilities, the facilities are found by a Regulatory Authority to be non-compliant with one or more GLP, GMP, GCP or current standards for pharmacovigilance practice compliance standards and such facilities are being used to conduct work under a Drug Discovery Plan or Development Plan, Isis will [***]. If requested by JBI, Isis will allow representatives of JBI to accompany Isis as part of any audit Isis conducts of [***] for which JBI exercises its Option.

1.3.8 **Supply of API for Drug Discovery**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis will supply (on its own or through a CMO), [***], (i) the non-GMP API necessary for Isis to select up to [***] lead Compounds for each Collaboration Target to advance to [***], plus (ii) up to [***] of non-GMP API for each of the lead Compounds selected for each Collaboration Target to support the formulation work under the Drug Discovery Plan prior to the designation of a Development Candidate. In addition, during the Drug Discovery Term, if requested by JBI, Isis will supply [***] up to [***] of ASO non-GMP API Isis has in its stock as of the Effective Date to support formulation activities under the Drug Discovery Plans, the selection of such non-GMP API to be in Isis' sole discretion. If additional quantities of non-GLP, non-GMP API are necessary to support such Drug Discovery Program activities, then JBI will purchase such API from Isis [***] for such non-GLP, non-GMP API, where [***] and [***] and where [***]. All such API provided by Isis will be [***] specific and [***] specific ASOs. If JBI desires API for ASOs that are specific to [***] then Isis will use Commercially Reasonable Efforts to design and supply such ASOs and JBI will pay Isis for such ASOs [***] and shall invoice JBI in accordance with Section 6.10.

1.3.9 **Supply of GLP Development Candidate and Clinical Supplies by Isis**. For the first Development Candidate for which JBI exercises its Option Isis will (on its own or through a CMO) supply [***] of API, not to exceed [***], to support the [***] and [***], where Isis will supply the [***] of such [***], and will, [***] supply the remainder of such [***] in [***] increments (or in [***] if, as a result of previous [***], the remaining material is [***]) if and when requested by JBI. For each additional Development Candidate for which JBI exercises its Option, Isis, [***], will (on its own or through a CMO) supply in [***] a [***] of API, not to exceed [***], to support the [***] and [***]. Except for the [***] of API for the first Development Candidate for which JBI has exercised its Option, JBI will [***] for such API [***], of which [***] within [***] days of [***]. JBI will take possession of such requested API no later than [***] days following Isis' release of such API.

1.4 **Program Costs and Expenses**. Except as expressly set forth below or elsewhere in this ARTICLE 1, each Party will be responsible for the costs and expenses incurred by it or on its behalf in the performance of the Drug Discovery Program activities for which such Party is responsible under the applicable Drug Discovery Plan and Development Plan.

1.5 **Drug Discovery Term; Extension**.

1.5.1 **Drug Discovery Term**. The term for the conduct of the Drug Discovery Programs will begin on the Effective Date and, subject to extension in accordance with Section 1.5.2 and/or earlier termination of this Agreement in accordance with ARTICLE 10 hereof, will end upon the earlier of (i) such time as the Options with respect to all Drug Discovery Programs either have been exercised by JBI or have expired unexercised, and (ii) the [***] anniversary of the Effective Date (the ***"Drug Discovery Term"***), *provided however*, that if Isis has delivered a Development Candidate Data Package to JBI for a Drug Discovery Program prior to the [***] anniversary of the Effective Date but the Option Period for such Drug Discovery Program has not expired as of the [***] anniversary of the Effective Date, the Drug Discovery Term will extend for that Drug Discovery Program only, until the earlier of (a) JBI's exercise of such Option and (b) expiration of such Option Period. Such extension shall not be subject to the extension fee as defined in Section 1.5.2 below.

1.5.2 **Extension of Drug Discovery Term**. JBI will have the right, in its discretion, to extend the Drug Discovery Term (i) for an additional [***] period if such extension applies to more than just the [***] Collaboration Target (not to exceed [***]), or (ii) for one additional [***] period if such extension only applies to the [***] Collaboration Target (not to exceed [***]), in each case by delivering a written notice of extension to Isis and paying Isis an extension payment of $[***] per extension no later than [***] days prior to the end of the then-applicable Drug Discovery Term.

1.5.3 **Consequences of End of Drug Discovery Term**. From and after the end of the Drug Discovery Term (including any extensions thereof), (i) Isis will have no obligation to perform any further activities for any Drug Discovery Program; (ii) any Drug Discovery Programs that have not reached the Development Candidate stage will no longer be Drug Discovery Programs and the applicable gene targets associated therewith will no longer be Collaboration Targets; (iii) Isis' obligations and JBI'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 Drug Discovery 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 either Party's rights or obligations under this Agreement with respect to any Drug Discovery Program for which JBI exercised its Option before the end of the Drug Discovery Term, including, but not limited to, the Parties' respective rights and obligations under ARTICLE 2, ARTICLE 4, ARTICLE 5 and ARTICLE 6 hereof.

1.5.4 **Carryover Development Candidates**. If, despite Isis' Commercially Reasonable Efforts, by the end of the Drug Discovery Term, Isis has not designated a Development Candidate for a particular Drug Discovery Program, then if at any time during the [***] following 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 Drug Discovery Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a ***"Carryover Development Candidate"***), then, Isis will notify JBI and will provide JBI with the data package presented to Isis' RMC to approve such Carryover Development Candidate. JBI will then have [***] 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, including the payment of the fee for [***] if not already paid by JBI (except that no additional option fee under Section 6.1 will be due). If, within [***] days after JBI's receipt of such notice from Isis, JBI 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 JBI either notifies Isis that it declines the offer for such Carryover Development Candidate, or JBI does not provide Isis with written notice during such [***]-day period that JBI 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.

1.6 Program Management.

1.6.1 **JRC**. The Parties will establish a joint research committee (the "***JRC***") to provide advice and make recommendations on the conduct of activities under each Drug Discovery Program. The JRC will consist of three representatives appointed by Isis and three representatives appointed by JBI. Each JRC member will be a senior scientific staff leader or have other experience and expertise appropriate for the stage of development of the Drug Discovery 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 JRC. The co-chairs will be responsible for overseeing the activities of the JRC consistent with the responsibilities set forth in Section 1.6.2. SCHEDULE 1.6.1 sets forth certain JRC governance matters agreed to as of the Effective Date. The JRC will determine the JRC operating procedures at its first meeting, including the JRC's policies for replacement of JRC members, policies for participation by additional representatives or consultants invited to attend JRC meetings, and the location of meetings, which will be codified in the written minutes of the first JRC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JRC meetings.

1.6.2 **Role of the JRC**. Without limiting any of the foregoing, subject to Section 1.6.3, the JRC will perform the following functions, some or all of which may be addressed directly at any given JRC meeting:

(a) maintain the list of Collaboration Targets, as such list may be updated from time to time in accordance with this Agreement, and attach such list to the minutes of the next JRC meeting following the designation of any additional Collaboration Target;

(b) review and approve the Drug Discovery Plan for each Program;

(c) review the overall progress of the Parties' efforts to achieve [***] with respect to each Drug Discovery Program;

(d) review the overall progress of Isis' efforts to discover, identify, optimize and select the Development Candidate for each Drug Discovery Program;

(e) review the overall progress of the Parties' efforts with respect to each the Drug Discovery Plan;

(f) amend each Drug Discovery Plan for each Drug Discovery Program,

(g) such other review and advisory responsibilities as may be assigned to the JRC pursuant to this Agreement.

1.6.3 **Decision Making**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JRC regarding the conduct of each Drug Discovery Program. Subject to Section 1.3.1 and Section 1.3.5, (i) Isis will have the final decision-making authority regarding [***] and whether to accept and how to implement the JRC's recommendations, and (ii) JBI will have the final decision-making authority regarding [***]; *provided that,* in each case, such decisions and conduct are in accordance with the applicable Drug Discovery Plan and do not increase the cost of the other Party. Except as otherwise permitted by Section 1.3.2, Section 1.3.5 and, the JRC 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.

1.6.4 **Term of the JRC**. Isis' obligation to participate in the JRC, or any of its subcommittees, will terminate upon JBI's exercise (or expiration) of the Option for the last Drug Discovery Program.

1.6.5 **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 JRC and performing the activities listed in SCHEDULE 1.6.5.

1.6.6 **Information Sharing Committee.** Formation and Purpose: Within [***] days after the [***], the Parties will establish an Information Sharing Committee (the "ISC") to review the Development of Product. The ISC will review and discuss the Development activities to be undertaken with respect to the Product being Developed by JBI and will provide a forum for Isis to provide input into such Development activities. Specific Responsibilities of the ISC: As part of its overall responsibilities, the ISC will: review the progress of the Development Plan; review any changes to the Development Plan; actively seek Isis input and consider all input in good faith; and perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties

1.6.7 **ISC Meetings**: The ISC will meet at least annually or on an *ad hoc* basis. The first meeting of the ISC will be held as soon as reasonably practicable, but in no event later than [***] days after formation. Meetings will be held at such place or places as are mutually agreed or by teleconference or videoconference. The ISC meetings will be chaired by JBI. The chairperson of the ISC will be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting of the ISC, and preparing and issuing minutes of each meeting within [***] days thereafter; provided however, that an ISC chairperson will call a meeting promptly upon the request by Isis to convene an ISC meeting. The minutes will not be finalized until both Parties review and approve them. Each Party will bear its own costs, including travel expenses, incurred by its ISC members or by any additional non-member participants of a Party in connection with their attendance at ISC meetings and other activities related to any ISC. Notwithstanding Section 1.6.6 and the foregoing provisions of this Section 1.6.7, with respect to Isis, the formation of the ISC and participation in the ISC are rights but not obligations that Isis may cancel for any Product at any time.

1.6.8 **Reduction of ISC Reporting**. If JBI declines to pursue any Follow-On Compounds targeting a particular Collaboration Target and Isis pursues a Follow-On Compound for such Collaboration Target, the ISC shall cease all ISC reporting activities relating to Products that modulate such Collaboration Target.

1.7 **Materials Transfer.** To facilitate the activities under the Drug Discovery Programs, either Party may provide certain materials for use by the other Party. All such materials will be used by the receiving Party in accordance with terms 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 except with 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.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1 **Exclusivity; Right of First Negotiation**.

2.1.1 **Exclusivity Covenants**.

(a) **The Parties' Exclusivity Covenants for Collaboration Targets During the Option Period**. 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 10.3.2 or Section 10.3.4, 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 of the applicable Option Period or the earlier termination of the applicable Option.

(b) **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 10.3.2 or Section 10.3.4, if JBI 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 [***] for a Product targeting such Collaboration Target; 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 [***] with respect to such Collaboration Target.

(c) **JBI's Exclusivity Covenant After Option Exercise**. After Option exercise, JBI's exclusivity obligations under Section 2.1.1(a) will be extended and will continue for so long as and to the extent of Isis' exclusivity obligations under Section 2.1.1(b), and except as otherwise described in Section 2.1.3.

2.1.2 **Right of First Negotiation for Follow-On Compounds**. On a Drug Discovery Program-by-Drug Discovery Program basis, during the period commencing on the date JBI exercises the applicable Option in accordance with this Agreement and ending upon [***] (such period, the "***ROFN Period***"), Isis hereby grants to JBI 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) At any time prior to the [***] following the [***] for the applicable Product, JBI may provide Isis with a non-binding, good faith written notice expressing JBI's desire for Isis to identify a Follow-On Compound (a "***Follow-On Interest Notice***"). If (i) JBI does not provide Isis with a Follow-On Interest Notice before the [***] following the [***] for the applicable Product, or (ii) JBI 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 [***] for the applicable Product, 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 [***], 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 JBI (a "***Follow-On Negotiation Notice***"), which notice [***]. Isis will not enter into such a Follow-On Agreement with any Third Party until the earlier to occur of: (A) [***] (each, a "***ROFN Termination Event***").

(b) Following a ROFN Termination Event, subject to JBI's right under Section 1.6.8 to stop sharing information, Isis will have no further obligation to negotiate with JBI 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. Any Follow-On Agreement entered into by Isis with a Third Party in accordance with this Section 2.1.2(b) will be a Permitted License to the extent related to the Follow-On Compound.

2.1.3 **Limitations and Exceptions to Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, each Party's practice of the following will not violate Section 2.1.1 and/or Section 2.1.2:

(a) Any activities conducted pursuant to the Prior Agreements as in effect on the Effective Date; provided, [***];

(b) The granting by Isis of, or performance of obligations under, Permitted Licenses;

(c) Up to and including the date of the [one year anniversary following the Option Period for a designated Collaboration Target, JBI may acquire, by license or otherwise, any Third Party asset that modulates a Collaboration Target so long as such Third Party asset has at least entered a Phase II Clinical Trial at the time of such acquisition; and

(d) After the date of the [***] for a designated Collaboration Target, JBI may [***], any Third Party [***] so long as such Third Party [***].

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 Autoimmune Diseases of the gut. Isis and JBI 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 any gene that is ***not*** a Collaboration Target for any indication, even if such products are designed to treat Autoimmune Disease.

ARTICLE 3.
EXCLUSIVE OPTION

3.1 **Option Grant and Option Deadline**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis hereby grants to JBI with respect to each Drug Discovery Program an exclusive option to obtain the license set forth in Section 4.1.1 with respect to such Drug Discovery Program (each an "***Option***"). JBI (i) shall provide Isis with written notice of its intent to exercise its Option within [***] days of receipt of the Development Candidate package for the application Drug Discovery Program and (ii) JBI shall pay the Option Fee described in Section 6.4 no later than the [***] day following JBI's notice of its intent to exercise its Option (the "***Option Deadline***").

3.2 **Effect of Option Exercise or Expiration**. If, by the Option Deadline, JBI 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 6.4, Isis will, and hereby does, grant to JBI or its designated Affiliate the license set forth in Section 4.1.1. If, by the applicable Option Deadline, JBI or its designated Affiliate has not both (y) provided Isis a written notice stating that JBI is exercising its Option, and (z) paid Isis the license fee in accordance with Section 6.4, then JBI's Option for the applicable Drug Discovery Program will expire.

ARTICLE 4.
LICENSE GRANTS

4.1 License Grants to JBI.

4.1.1 Development and Commercialization License. Subject to the terms and conditions of this Agreement, on a Drug Discovery Program-by-Drug Discovery Program basis, effective upon JBI's exercise of the Option for a particular Drug Discovery Program in accordance with this Agreement, Isis grants to JBI (i) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Drug Discovery Program in the Field, and (ii) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology other than the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Drug Discovery Program in the Field. The grant described in subsection (ii) in no way limits Isis' ability to grant additional licenses to Third Parties under the Licensed Technology, other than the Isis Product Specific Patents, to Research, Develop, Manufacture, have Manufactured register, market and Commercialize Third Party products that are not Product(s).

4.1.2 Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, JBI 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, Isis Formulation Patents and Isis Know-How, to an Affiliate of JBI 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, JBI 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, JBI hereby grants Isis the right to enforce such sublicense terms on JBI's behalf and will cooperate with Isis (which cooperation will be at JBI's sole expense and will include, JBI 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. JBI will provide Isis with a true and complete copy of any sublicense granted pursuant to this Section 4.1.2 within [***] days after the execution thereof.

(b) In connection with [***], or supply API and Finished Drug Product for Commercialization, Isis will, at JBI's option, either (1) [***], which Isis agrees it will [***], or, (2) permit JBI to [***]. Each such manufacturing agreement between JBI and [***] will contain provisions permitting Isis to elect to have such agreements assigned to Isis to the extent such agreement relates to the applicable Clinical Supplies or Finished Drug Product in the event of a termination of this Agreement with respect to a particular Drug Discovery Program. JBI will provide Isis with a true and complete copy of any manufacturing agreement entered into with [***] within [***] 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 [***] days after written notice from JBI specifying the details of any such failure, JBI will have the right to grant a sublicense under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How 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 JBI; *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 JBI, 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 JBI. JBI 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 JBI under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to JBI Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by JBI 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 6.9, 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 JBI in writing (or via electronic data room) prior to JBI's exercise of the applicable Option. Isis will disclose to JBI any Third Party Obligations Isis believes apply to applicable Products each time [***], and JBI 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, JBI 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 JBI 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**. JBI or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.3, 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 JBI has (a) exercised its Option for a particular Product and obtained the license under Section 4.1.1, and (b) [***], then following review and consideration by each Party's patent representatives, Isis will assign to JBI or one or more of its designated Affiliates, Isis' ownership interest in (i) all Isis Product-Specific Patents related to such Product 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 such Product, 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 JBI paying Isis the milestone for Completion of a PoC for the applicable Product.

4.2.2 JBI grants to Isis a fully-paid, royalty-free, worldwide, exclusive, sublicensable license under any Isis Product Specific Patents and Jointly-Owned Program Patents assigned to JBI under Section 4.2.1, (i) [***], (ii) to [***] and (iii) to [***] to the extent permitted by this Agreement.

4.3 **Subcontracting**. Subject to the terms of this Section 4.3, 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.

4.4 **Technology Transfer after Option Exercise**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis will promptly, but no later than [***] days after JBI exercises its Option for such Drug Discovery Program hereunder, deliver to JBI or one or more designated Affiliates:

4.4.1 **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 10.3.2, including transferring the IND for the applicable Development Candidate to JBI together with all regulatory documentation (including drafts) related to the applicable Development Candidate.

4.4.2 **Isis Manufacturing and Analytical Know-How**. Solely for use by JBI, its Affiliates or a Third Party acting on JBI's behalf to Manufacture API in JBI'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 JBI, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1, in each case solely to Manufacture API, Clinical Supplies or Finished Drug Product in accordance with the terms of this Agreement.

4.4.3 **Isis Contribution of FTEs for Know-How Transfer.** Isis will provide up to [***] hours of its time [***] to JBI for each Drug Discovery Program to transfer such Isis Know-How and Manufacturing and Analytical Know-How under Section 4.4.1 and Section 4.4.2. Thereafter, if requested by JBI, Isis will provide JBI with a reasonable level of assistance in connection with such transfer, which JBI will reimburse Isis for its time incurred in providing such assistance at [***] incurred by Isis in providing such assistance and shall invoice JBI in accordance with Section 6.10.

4.4.4 **API and Product**. Upon JBI's written request, Isis will sell to JBI any bulk API in Isis' possession at the time of Option exercise, at a price equal to [***].

4.5 **Cross-Licenses Under Program Technology.**

4.5.1 **Enabling Patent Licenses from JBI to Isis.** Subject to the terms and conditions of this Agreement (including Isis' exclusivity obligations under Section 2.1.1), JBI hereby grants Isis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any JBI Program Technology to research, develop, manufacture, have manufactured and commercialize [***].

4.5.2 **Enabling Patent Licenses from Isis to JBI.** Subject to the terms and conditions of this Agreement (including JBI's exclusivity obligations under Section 2.1.1), Isis hereby grants JBI a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any Isis Program Technology to research, develop, manufacture, have manufactured and commercialize [***].

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1 **JBI Diligence**. Following an Option exercise, JBI 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 JBI will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize in each and every Major Market at least one Product from each Drug Discovery Program for which an Option has been exercised.

5.2 **Specific Performance Milestone Events**. Without limiting any of the foregoing, following an Option exercise, JBI will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.2 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in SCHEDULE 5.2; *provided, however*, if [***].

5.3 **Integrated Development Plan**. On a Product-by-Product basis, JBI will prepare a Development and global integrated Development plan outlining key aspects of the Development of each Product through Approval (each, an "***Integrated Development Plan***" or "***IDP***"). JBI will prepare the IDP no later than [***] after [***], and the IDP will contain information consistent with JBI's Development plans for its similar products at similar stages of development. Once JBI has prepared such plans, JBI will update the IDP consistent with JBI's standard practice and provide such updates to Isis annually via the ISC.

5.4 **Regulatory**.

5.4.1 **Ownership of and Assistance with Regulatory Filings**.

(a) For each Product for which JBI has exercised its Option, JBI will be the sponsor and will be responsible for filing the IND. Once a Development Candidate is designated under this Agreement, the JRC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND.

(b) [***] begin to prepare a plan, 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). The Parties will act in good faith and mutually agree upon each such plan, *provided, however*, that, after exercising an Option for the applicable Drug Discovery Program, JBI will have final decision making authority with respect to the contents of such plan that do not require Isis' participation.

(c) [***] regulatory filings for the Product, [***] and JBI, including [***] plus any reasonable [***] providing such assistance and will specify that JBI will [***] designated responsibilities in connection with the applicable regulatory filing [***] in accordance with Section [***]; provided there will be no additional [***] conducted under a Development Plan where [***].

5.4.2 **[***] Meetings with FDA**. For each Product, JBI shall [***] meetings with the FDA to discuss (i) pre-IND filing matters; (ii) end of Phase II matters; or (iii) pre-NDA filing matters. [***].

5.4.3 **[***] Regulatory Meetings**. JBI will [***] of any meetings JBI has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product or that directly relate to [***], and may allow [***]. In addition, JBI will provide Isis with as much advance written notice as practicable of any [***] Regulatory Authorities, and JBI [***].

5.4.4 **Regulatory Communications**. [***], JBI [***] provide Isis with copies of documents and communications submitted to, or received from, Regulatory Authorities [***] that materially impact the Development or Commercialization of Products for [***], and JBI will [***] such documents and communications.

5.4.5 **Class Generic Claims**. To the extent JBI intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, JBI will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

5.4.6 **End of Obligations if [***]**. JBI's obligations under Section 5.4.2, Section 5.4.3, and Section 5.4.4 will cease with respect to a particular Product if [***].

5.5 **Applicable Laws**. JBI will use commercially reasonable efforts perform its activities pursuant to this Agreement in compliance with GLP, GCP and GMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.6 **Isis' Antisense Safety Database**.

(a) JBI will provide Isis with copies of [***] and the [***] within [***] days following the date such information is [***], as applicable. JBI will [***]. All such information disclosed by JBI to Isis will be JBI Confidential Information. JBI will deliver all such information 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). JBI will also cause its Affiliates and Sublicensees to comply with this Section 5.6(a).

(b) During the term of this Agreement, if requested by JBI, JBI and Isis will [***].

ARTICLE 6. FINANCIAL PROVISIONS

6.1 **Option Fee**. In partial consideration for JBI's Options hereunder, within five Business Days following the Effective Date, JBI will pay Isis an Option fee equal to $10,000,000 for each of the three Drug Discovery Programs for an aggregate payment of $30,000,000.

6.2 **Fourth Target Fee**. If JBI elects to designate a fourth target, JBI will pay Isis $[***] within [***] days of JBI's written notice to Isis designating such target.

6.3 **Milestone Payments for Achievement of Pre-Licensing Milestone Event**. As further consideration for JBI's Options and Licenses hereunder, on a Collaboration Target-by-Collaboration Target basis, JBI will pay to Isis a milestone payment of $[***] for achievement of [***] for such Collaboration Target (each, a "***Pre-Licensing Milestone Event***"). Isis shall provide JBI with written notice of achievement of [***] and JBI shall make such payment within [***] days of receipt of such notification. With respect to [***], the Parties agree that [***] is deemed to have been achieved so that Isis may [***], and JBI will make the associated payment under this Section 6.3 within [***] days of the Effective Date; provided such payment does not limit the Parties' obligation to conduct the activities set forth in the Drug Discovery Plan for [***].

6.4 **License Fee**. On an Option-by-Option basis, together with JBI's written notice to Isis stating that JBI is exercising the Option with respect to the Drug Discovery Program for a Collaboration Target in accordance with this Agreement, JBI will pay to Isis the applicable one-time license fee set forth in TABLE 1 below (each, a "***License Fee***"):

TABLE 1

Option	License Fee
[***]	$[***]
[***]	$[***]

6.5 **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Drug Discovery Program-by-Drug Discovery Program basis, JBI will pay to Isis the applicable milestone payment set forth in TABLE 2 below for the first achievement of the corresponding milestone event in TABLE 2 (each, a *"**Post-Licensing Milestone Event**"*) by the first Product against such Collaboration Target to achieve such Post-Licensing Milestone Event:

TABLE 2

Post-Licensing Milestone Event	Milestone Event Payment
[***]	$[***]
[***]	$[***]
[***]*	$[***]*
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

*[***].

6.6 **Limitations on Milestone Payments; Exceptions; Notice**.

6.6.1 Each milestone payment set forth in TABLE 2 above will be paid only once per Drug Discovery Program upon the first achievement of the applicable Post-Licensing Milestone Event, regardless of how many Products under a Drug Discovery Program achieve such Milestone Event.

6.6.2 If a particular Post-Licensing 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 the next Post-Licensing Milestone Event to be achieved, the Post-Licensing Milestone Event payment applicable to such earlier Post-Licensing 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.

6.6.3 Each time a Post-Licensing Milestone Event is achieved under this ARTICLE 6, JBI will send Isis, or Isis will send JBI, 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.

6.7 **Net Sales Milestone Payments**. On a Drug Discovery Program-by-Drug Discovery Program basis, for the first Calendar Year in which Annual worldwide Net Sales of the first Product progressed from a Drug Discovery Program that achieves or exceeds each of the levels of Annual worldwide Net Sales set forth in TABLE 3 below (each, a "***Sales Milestone Event***"), JBI will pay Isis the corresponding one-time Sales Milestone Event payment within [***] days of the end of the Calendar Quarter during such Calendar Year in which such Sales Milestone Event occurs. \

TABLE 3

Annual Worldwide Net Sales	Sales Milestone Event Payment
≥ $[***]	$[***]
≥ $[***]	$[***]
≥ $[***]	$[***]

Each Sales Milestone Event payment set forth in TABLE 3 above will be due only one time per Drug Discovery Program, for the first Calendar Year in which the corresponding Sales Milestone Event occurs. If more than one of the above Sales Milestone Events is achieved in the same year, JBI will pay all applicable milestone payments.

6.8 **Royalty Payments to Isis**.

6.8.1 **JBI Royalty**. As partial consideration for the rights granted to JBI hereunder, subject to the provisions of this Section 6.8.1 and Section 6.8.2, JBI will pay to Isis royalties on a Product-by-Product basis, on Annual worldwide Net Sales of Products included in the applicable Drug Discovery Program sold by JBI, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 4 below (the "***JBI Royalty***"):

TABLE 4

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 ≥ $[***]	[***]%

(a) Annual worldwide Net Sales will be calculated by [***].

(b) For purposes of clarification, any Isis Product-Specific Patents and Jointly-Owned Program Patents assigned to JBI as set forth in Section 4.2.1 will still be royalty-bearing and considered Isis Product-Specific Patents and Jointly-Owned Program Patents, respectively, for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.8.2 **Application of Royalty Rates**. All royalties set forth under Section 6.8.1 are subject to the provisions of this Section 6.8.2, and are payable as follows:

(a) **Royalty Period**. JBI's obligation to pay Isis the JBI Royalty above with respect to Products will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product in a country until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents or Program Patents Covering such Product in the country in which such Product is made, used or sold, [***] (such royalty period, the "***Royalty Period***").

(b) **Royalty Reduction – U.S. Loss of Patent Rights.** If (i) there is no longer a Valid Claim within the Licensed Patents or Program Patents Covering a Product in the U.S., and [***], then JBI may reduce the royalty payments for sales in the U.S. described in Table 4 by [***] ([***]) percent. JBI shall make the reduced royalty payments to Isis for the remainder of the Royalty Period.

(c) **Royalty Reduction – Early Generic Product Entry.** If after the [***] anniversary of the First Commercial Sale of a Product, in a given country within the Territory, entry of a Generic Product has occurred prior to the expiry of the last Licensed Patent or Program Patent with a Valid Claim covering a Product, and either (i) subsequently the sales of the Product have declined by [***] percent ([***]%) or more but less than [***] percent ([***]%) as compared to the [***] Calendar Quarters [***] prior to such Generic Product entry, then JBI may reduce the royalty payments for sales in such country described in Table 4 by [***] percent ([***]%), or (ii) subsequently the sales of the Product have declined by [***] percent ([***]%) or more as compared to the [***] Calendar Quarters [***] prior to such Generic Product entry, then no further royalty payments shall be due to Isis for such Product in such country; provided, if JBI reduced or ceased paying the royalty payments under this Section, and thereafter a court of competent jurisdiction determines that the Licensed Patent is valid and infringed by the Generic Product, JBI shall resume making royalty payments at the full amount as of the date of such court order.

(d) **Limitation on Aggregate Reduction for JBI Royalties**.

(i) In no event will the aggregate royalty offsets under Section 6.9.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to [***]% of the JBI Royalty rates listed in TABLE 4.

(ii) In addition, in no event will the aggregate royalty offsets and reductions under Section 6.8.2(c) (as applicable) and Section 6.9.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to less than [***].

(e) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis JBI's obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Royalty Period at which time JBI will have a fully paid up license under the Licensed Patents; provided [***].

6.9 **Third Party Payment Obligations**.

6.9.1 **Existing Isis In-License Agreements**.

(a) Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to JBI under Section 4.1.1 was in-licensed or was acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.9.1 (all such license or purchase agreements being the "***Isis In-License Agreements***"). Certain license fees, maintenance fees, milestone payments, royalties or similar payments that apply to Products 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 JBI under this Agreement.

(b) Any payment obligations arising under the Isis In-License Agreements as existing on the Effective Date and up until JBI exercises an Option under this Agreement, as they apply to the Isis Core Technology used by Products developed under this Agreement will be paid by [***], and [***], as [***]. In the event JBI determines that it wishes to obtain a sublicense under the Isis In-License Agreements, [***].

6.9.2 **New In-Licensed Isis Product-Specific 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 JBI under Section 4.1.1 if JBI agrees in writing to pay Isis (i) [***] and (ii) [***]. In the event JBI declines to pay Isis [***], nothing in this Agreement [***].

6.9.3 Additional Core IP In-License Agreements.

(a) JBI will promptly provide Isis written notice of any Additional Core IP JBI 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 JBI under Section 4.1.1, and any financial obligations under such Third Party agreement will be [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify JBI, and JBI may obtain such a Third Party license and, subject to Section 6.8.2(d), JBI may offset an amount equal to [***]% of any [***] paid by JBI 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 JBI pursuant to Section 6.9.3(a) is Additional Core IP under Section 6.9.3(b), Isis will send written notice to such effect to JBI, 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 JBI is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.9.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

6.9.4 Other Third Party Payments.

(a) **Isis' Third Party Agreements**. Except as otherwise expressly agreed to by JBI under Section 6.9.2, after Option exercise, JBI will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Isis.

(b) **JBI's Third Party Agreements**. Without limiting any applicable [***] under Section 6.9.3(b), JBI will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by JBI as they apply to Products.

6.10 **Invoices.** Unless otherwise specified hereunder, JBI shall make payments required hereunder to Isis within [***] ([***]) days from the date an invoice is received by JBI provided that any invoiced costs are for fees or services that have been rendered by Isis plus Out of Pocket Expenses incurred by Isis and further subject to the invoice having been received by JBI. All invoices must reference a valid Purchase Order (PO) Number which JBI shall provide to Isis within [***] ([***]) days of any such contracted service after the Effective Date. Isis' invoices will include Isis' good faith estimate of the FTE cost incurred by Isis in performing the services and the amount of Out-of Pocket Expenses incurred and charged by Isis. Before Isis commences work, JBI and Isis will agree to a budget for the work JBI requests Isis to perform that will include Isis' good faith estimate of the FTE cost plus Out of Pocket Expenses. Isis shall provide reasonable support for each invoice. Reasonable support means [***]. Invoices shall be sent to: Johnson & Johnson Shared Services, P.O. Box 16540, New Brunswick, NJ 08906-6540, United States, with a copy to Immunology TA Controller, c/o J&J PRD, PO Box 766, Welsh & McKean Road, Spring House 19477, or via www.ap.jnj.com if Isis is established with a web invoice account. JBI reserves the right to return to Isis unprocessed and unpaid those invoices that do not reference a valid P.O. number.

6.11 Payments.

6.11.1 Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, JBI will make royalty payments to Isis under this Agreement within [***] days following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report showing on a Product-by Product and country-by-country basis the gross sales, the Net Sales, and a calculation of the amount of royalty due on such Net Sales. This report shall also include the exchange rates and other methodology used in converting Net Sales into US dollars from the currencies in which sales were made in order to determine the appropriate royalty tier and royalty. If no royalties are payable in respect of a given Calendar Quarter, JBI will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, on a Product-by-Product basis, beginning with the Calendar Quarter in which the First Commercial Sale for such Product is made and for each Calendar Quarter thereafter for the next [***] ([***]) years, JBI will (based on information JBI collects, and in a format JBI uses for its own internal planning and reporting purposes) provide Isis a preliminary non-binding report estimating the total Net Sales of, and royalties payable to Isis for Products projected for such Calendar Quarter. JBI will endeavor to provide such preliminary non-binding report within [***] Business Days following the end of each such Calendar Quarter; provided JBI will provide such preliminary non-binding report no later than [***] Business Days following the end of each such Calendar Quarter.

6.11.2 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. With respect to sales of Product invoiced in a currency other than USD, such amounts and the amounts payable hereunder shall be expressed in their USD equivalent calculated as follows: For the upcoming Calendar Year, JBI shall provide: 1) a Currency Hedge Rate(s) to be used for the local currency of each country of the Territory and 2) the details of such Currency Hedge Rate(s) in writing to Isis not later than [***] business days after the Currency Hedge Rate(s) are available from the GTSC or its Affiliates, which is customarily at the end of October. Such Currency Hedge Rate(s) will remain constant throughout the upcoming calendar year. JBI shall use the Currency Hedge Rate(s) to convert Net Sales to USD for the purpose of calculating royalties and Sales Milestones.

6.11.3 **Records Retention**. Commencing with the First Commercial Sale of a Product, JBI will keep complete and accurate records pertaining to the sale of Products for a period of [***] Calendar Years 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 JBI hereunder.

6.12 **Audits**. After Option exercise, during the Agreement Term and for a period of [***] Calendar Years thereafter, at the written request and expense of Isis, JBI will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to JBI, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records at the location where such records are maintained as may be necessary for the sole purpose of verifying the calculation and reporting of milestones and Net Sales, and the correctness of any milestone and royalty payments made under this Agreement for any period within the preceding [***] Calendar Years. As a condition to examining any records of JBI, such auditor will sign a nondisclosure agreement reasonably acceptable to JBI in form and substance. Any and all records of JBI examined by such independent certified public accountant will be deemed JBI's Confidential Information. The report of the independent public accountant shall be shared with JBI prior to distribution to Isis such that JBI can provide the independent public accountant with justifying remarks for inclusion in the report prior to sharing the conclusions of such independent public audit with Isis. Upon completion of the audit, the accounting firm will provide both JBI and Isis with a written report disclosing whether the royalty payments made by JBI are correct or incorrect, whether any milestone payment that became due during the audited period was timely reported and paid, and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of JBI, it is shown that JBI's royalty payments under this Agreement were less than the royalty amount which should have been paid, and/or that any milestone payment was not paid when due or at all, then JBI 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 [***] days of receiving the Audit Report, with interest calculated in accordance with Section 6.14. If, as a result of any inspection of the books and records of JBI, it is shown that JBI's payments under this Agreement were greater than the royalty amount which should have been paid, then JBI will receive a credit against future royalty payments due under Section 6.8 equal to the difference between the amounts paid by JBI and the royalty amounts which should have been paid. Isis will pay for such audit, except that if JBI is found to have underpaid Isis by more than [***]% of the amount that should have been paid, and/or not to have paid any milestone that should have been paid, JBI will reimburse Isis' reasonable costs of the audit.

6.13 **Taxes**.

6.13.1 **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.

6.13.2 Isis will provide JBI with any and all tax forms in advance of the due dates that may be reasonably necessary in order for JBI to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following JBI's timely receipt of such tax forms from Isis, JBI 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. 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 6.13.2.

6.13.3 JBI will make all payments to Isis under this Agreement without deduction or withholding for Taxes except to the extent that any such deduction or withholding is required by law in effect at the time of payment.

6.13.4 Any Tax required to be withheld on amounts payable under this Agreement will be paid by JBI on behalf of Isis to the appropriate governmental authority, and JBI will furnish Isis with proof of payment of such Tax. Any such Tax required to be withheld will be an expense of and borne by Isis. If any such Tax is assessed against and paid by JBI, then Isis will indemnify and hold harmless JBI from and against such Tax unless the assessment and payment of such Tax is a result of acts or omissions by JBI.

6.13.5 JBI and Isis will cooperate with one another and use reasonable efforts to lawfully avoid or reduce 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, including but not limited to all documentation required by any taxing authority or reasonably requested by either Party to secure a reduction in the rate of applicable withholding Taxes or similar obligations. Within five Business Days of the Effective Date of this Agreement, Isis will deliver to JBI an accurate and complete Internal Revenue Service Form W-9.

6.13.6 The provisions of this Section 6.13 Are to be read in conjunction with the provisions of Section 12.4 below.

6.14 **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.

6.15 **Paying Agent.** Janssen Research & Development, L.L.C., an Affiliate of JBI acting as a paying agent for JBI, may make certain payments due under this Agreement.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1 **Ownership**.

7.1.1 **Isis Technology and JBI 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 JBI will own and retain all of its rights, title and interest in and to the JBI Know-How and JBI 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, JBI is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of JBI or its Affiliates during the Drug Discovery Term ("***JBI Program Know-How***") and any Patent Rights that claim or cover JBI Program Know-How ("***JBI Program Patents***" and together with the JBI Program Know-How, the "***JBI Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by JBI 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 during the Drug Discovery Term ("***Isis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Isis Program Patents***" and together with the Isis Program Know-How, the "***Isis Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any assignment, rights or licenses expressly granted by Isis to JBI under this Agreement. Any Know-How discovered, developed, invented or created jointly during the Drug Discovery Term 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 JBI 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 JBI 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 7.1.3. Isis' obligation to participate in the JPC will terminate upon the end of the Drug Discovery Term. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. If the JPC dissolves, each Party will designate a patent attorney who will be responsible for intellectual property matters under this Agreement. A strategy will be discussed with regard to (i) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents that would be or are licensed to JBI under Section 4.1.1 in connection with a Product and JBI Product-Specific Patents, (ii) defense against allegations of infringement of Third Party Patent Rights, (iii) licenses to Third Party Patent Rights or Know-How, and (iv) the timing and subject matter of any potential publications regarding a Drug Discovery Program, 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 prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) 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 JBI) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such dispute, even after seeking the JRC'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.

(c) 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 7.1.3. The JPC will determine 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. Each party shall bear their own cost of participation on the JPC.

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.

7.2.2 Licensed Patents and JBI 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, Isis Manufacturing and Analytical Patents, and Isis Formulation Patents.

(b) Licensed Patents After Option Exercise. After JBI exercises its Option for a particular Drug Discovery Program, JBI will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Patents and Jointly-Owned Program Patents that cover Products under such Research project to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such Option exercise, 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) JBI Patents. JBI will control and be responsible for all aspects of the Prosecution and Maintenance of all JBI 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 are not Product Specific Patents. 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 that are Product Specific Patents and the subject of such Option. After exercise of an Option, JBI will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that are Product Specific Patents and are the subject of such exercised 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 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 JBI 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 JBI under this Agreement or the JBI Product-Specific Patents ("***JBI-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 JBI-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the JBI-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then JBI 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 JBI-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, JBI will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such JBI-Prosecuted Patent in such country in Isis' own name, but only to the extent that JBI is not required to take any position with respect to such abandoned JBI-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 JBI under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such JBI-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify JBI if Isis intends to abandon such JBI-Prosecuted Patent.

(c) 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 JBI of such intention at least 60 days before such Patent Right will become abandoned, and JBI 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 JBI assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 7.2.4(c), JBI will have no obligation to notify Isis if JBI intends to abandon such Isis Product-Specific Patent.

(d) 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.

(e) 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(e), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(f) 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 JBI 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 JBI 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, JBI 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) JBI 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. JBI 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 JBI 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 JBI 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 JBI 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 JBI with prompt written notice of the commencement of any such Proceeding, and Isis will keep JBI 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), JBI 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 the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation 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 JBI also enforces any Patent Rights Controlled by JBI being infringed that Cover the Product, then JBI will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding to enforce the Isis Product Specific Patents 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,* JBI will have the right to control such litigation. If JBI 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 JBI 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 JBI will have the right to be represented in any such action by counsel of its own choice at its own expense. 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, Isis Manufacturing and Analytical Patents, or Isis Formulation 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 JBI'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 JBI'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 Section 7.5.6 neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this 7.5.6 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 JBI 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, each Party will receive [***]% of such proceeds; 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 JBI**. JBI will retain all rights to pursue an infringement of any Patent Right solely owned by JBI which is other than a Competitive Infringement and JBI will retain all recoveries with respect thereto.

7.7 **Patent Listing**. JBI 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 JBI 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, JBI 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, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents, regardless of which Party owns such Patent Rights.

7.8 **Joint research agreement under the Leahy-Smith America Invents Act.** In the event that a Party intends to so invoke the Leahy-Smith America Invents Act, once agreed to by the other Party, it will notify the other Party and the Parties shall use reasonable efforts to cooperate and coordinate their activities with such Party 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 35 U.S.C. § 100(h)

7.9 **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this Section 7.9 will be subject to the Third Party rights and obligations under any (i) New Third Party License the restrictions and obligations of which JBI has agreed to under Section 6.9.2, (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 JBI hereunder and, this Agreement purports to grant any such rights to JBI, Isis will act in such regard with respect to such Patent Rights at JBI's direction.

7.10 **Additional Right and Exceptions**. Notwithstanding any provision of this Section 7.10, 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, JBI will determine which relevant patents will be extended.

7.12 **Rights in Bankruptcy.** 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.

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 Drug Discovery Program.

8.2 **Representations and Warranties of Isis**. Isis hereby represents and warrants to JBI, 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 JBI under Section 4.1.1 upon the exercise of the Option for a Product arising under the Drug Discovery 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 JBI to further Develop and Commercialize a Product.

8.2.2 Schedule 8.2.2(a), Schedule 8.2.2(b), Schedule 8.2.2(c) and Schedule 8.2.2(d) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Formulation Patents that apply to the Compounds contemplated under the Drug Discovery 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 JBI under this Agreement.

8.2.3 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 or Collaboration Targets that would prevent Isis from performing the activities under this Agreement or from granting JBI the licenses under Section 4.1. 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 or Collaboration Targets that would prevent Isis from performing the activities under this Agreement or from granting JBI the licenses under Section 4.1.

8.2.4 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.

8.2.5 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.

8.3 **Isis Covenants**. Isis hereby covenants to JBI that, except as expressly permitted under this Agreement:

8.3.1 Isis will promptly amend SCHEDULE 8.2.2(a), SCHEDULE 8.2.2(b) and SCHEDULE 8.2.2(c) and submit such amended Schedules to JBI 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 that Isis believes may become subject to a license from Isis to JBI for the Development Candidate under this Agreement;

8.3.3 Isis will promptly notify JBI 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 JBI to cure such breach on Isis' behalf upon JBI'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 JBI's rights hereunder without first obtaining JBI's written consent, which consent may be withheld in JBI's sole discretion; and

8.3.5 all of Isis' employees performing 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 as the sole owner thereof.

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. JBI 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 JBI**. JBI 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 JBI, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with JBI'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 JBI 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 JBI or its Affiliates or Sublicensees; or

9.1.4 the Commercialization of a Product by or on behalf of JBI 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 in each case for which Isis has an indemnity obligation pursuant to Section 9.2.

9.2 **Indemnification by Isis**. Isis will indemnify, defend and hold harmless JBI 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; or

9.2.3 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 JBI or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance, in each case for which JBI 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.

9.4.2 **JBI's Insurance Obligations**. JBI 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, JBI will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a clinical trials/product liability 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 [***] days before JBI initiates the First Commercial Sale of a Product hereunder. JBI will furnish to Isis evidence of such insurance upon request. Notwithstanding the foregoing, JBI 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 JBI'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 UNDER THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.3.4(a) BY JBI 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 the expiration of all payment obligations under this Agreement with respect to all Products in all countries; *provided, however,* that if every Option either (a) has expired as a result of JBI not providing Isis a written notice stating JBI is exercising such Option and paying Isis the applicable license fee under Section 6.4 by the applicable Option Deadline, or (b) has been terminated prior to Option exercise pursuant to Section 10.2.1 or 10.2.2, then this Agreement will expire on the expiration or termination, as applicable, of the last Option.

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 **JBI's Termination for Convenience**. At any time following payment by JBI of the upfront fee under Section 6.1, subject to Section 10.3.1 below, JBI will be entitled to terminate this Agreement as a whole, or terminate this Agreement in part with respect to a particular Drug Discovery Program and applicable Collaboration Target, for convenience by providing 90 days written notice to Isis of such termination.

10.2.2 Termination for Material Breach.

(a) **JBI's Right to Terminate**. If JBI believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.2.5, which is governed by Section 10.2.3 below), then JBI 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, JBI may terminate this Agreement as a whole, or terminate this Agreement in part with respect to the particular Program affected by such breach, and the applicable Collaboration Target, 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 Program affected by such breach and the applicable Collaboration Target.

(b) **Isis' Right to Terminate**. If Isis believes that JBI is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.2.5, Section 5.1 or Section 5.2, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to JBI. If the breach is curable, JBI 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 JBI 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 Drug Discovery Program(s) and the applicable Collaboration Target(s) affected by such breach by providing written notice thereof to JBI. To the extent such material breach is uncured for one Drug Discovery Program, the remaining active Drug Discovery Programs for which there is no uncured material breach shall remain in effect.

10.2.3 Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Isis, in JBI's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.2.5 prior to Option exercise with respect to a particular Drug Discovery Program or with respect to other agreed-upon activities to be performed by Isis associated with the research, Development, or Commercialization of a Product, under this Agreement, JBI will notify Isis and, within 30 days thereafter, Isis and JBI 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 1.2.5 or for activities otherwise agreed upon by Isis under this Agreement. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by Section 1.2.5 with respect to such Drug Discovery Program, then subject to Section 10.2.4 below, JBI will have the right to terminate this Agreement as it relates to the applicable Drug Discovery Program.

(b) If JBI, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 1.2.5, Section 5.1 or Section 5.2 with respect to a Product or Drug Discovery Program above, Isis will notify JBI and, within 30 days thereafter, Isis and JBI 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 JBI's use of Commercially Reasonable Efforts in Section 1.2.5, Section 5.1 or Section 5.2. Following such a meeting, if JBI fails to use Commercially Reasonable Efforts with respect to the applicable Product or Drug Discovery Program as contemplated by Section 1.2.5, Section 5.1 or Section 5.2, then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement as it relates to such Product or Drug Discovery Program.

10.2.4 **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 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 10.2.2 or Section 10.2.3, 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.

10.2.5 **Termination for Patent Challenge**. Isis may terminate this Agreement, if JBI disputes, [***] validity [***], provided however that, [***] Isis shall not have the right to terminate if [***]:

(a) JBI asserts invalidity as a defense in any court proceeding bought by Isis asserting infringement of a granted Patent within the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or [***]; or

(b) JBI (i) acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a granted Patent within the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents or (ii) licenses a product for which Isis has an existing challenge, whether in a court or administrative proceeding, against [***].

10.2.6 **Termination for Insolvency**. 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.

10.3 **Consequences of Expiration or Termination of the Agreement**.

10.3.1 **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 Drug Discovery 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 Drug Discovery 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) **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.

(c) **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 6.11.3 (Records Retention), Section 6.12 (Audits), Section 7.1.1 (Isis Technology and JBI Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.5 (Termination for Insolvency), Section 10.3 (Consequences of Expiration or Termination of the Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.3.2 **Perpetual, Royalty-Free Non-Exclusive License**. If JBI has exercised its Option for a particular Drug Discovery Program, then upon expiration of the Royalty Period in all countries in which the applicable Products are being or have been sold, Isis will and hereby does grant to JBI 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 Drug Discovery Program.

10.3.3 **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 10.3.1, the following terms will apply to each Drug Discovery Program that is the subject of such expiration or termination:

(a) JBI's Option under Section 3.1 will expire and Isis will be free to Develop and Commercialize Compounds included in such Drug Discovery Program 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 Drug Discovery Program(s).

(c) To the extent requested by Isis, JBI will promptly transfer to Isis all data, results and information (including JBI's Confidential Information and any regulatory documentation (including drafts)) related to the terminated Drug Discovery Program(s) in the possession of JBI and its contractors to the extent such data, results and information were generated by or on behalf of JBI under this Agreement.

(d) Except as explicitly set forth in Section 10.3.1(a), Section 10.3.1(b) or Section 10.3.1(c), JBI will have no further rights and Isis will have no further obligations with respect to each terminated Drug Discovery Program.

10.3.4 **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 10.3.1, the following terms will apply to any Pre-Clinical Development Program that is the subject of such termination:

(a) The applicable licenses granted by Isis to JBI under this Agreement will terminate and JBI, 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 Pre-Clinical Development Program(s).

(c) Except as explicitly set forth in Section 10.3.1(a), JBI will have no further rights and Isis will have no further obligations with respect to the terminated Pre-Clinical Development Program.

(d) If (y) JBI terminates the Agreement under Section 10.2.1 (JBI's Termination for Convenience) or (z) Isis terminates this Agreement under Section 10.2.2(b) (Isis' Right to Terminate) or Section 10.2.3 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply *solely with respect to the terminated* Pre-*Clinical Development Program(s)*:

(i) JBI will grant to Isis a sublicensable, worldwide, royalty bearing exclusive license or sublicense, as the case may be, to all JBI Technology Controlled by JBI 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) For each Discontinued Product for which JBI, its Affiliate or Sublicensee has [***], Isis or any sublicensee or collaborator shall pay to JBI a royalty on net sales made by Isis or its Affiliates or sublicensee of such Discontinued Product according to the following: (a) if neither [***] prior to termination: [***]% of Net Sales, (b) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales, (c) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales, and (d) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales; provided (A) if (i) Isis enters an arms-length license agreement with a Third Party with respect to a Discontinued Product and (ii) the definition of Net Sales is different in such license agreement than as described above, then, the Parties will use the definition described in the Third Party license for the calculation of royalties under this Section 10.3.4(d)(ii); and (B) Sections 6.8.2, 6.10, 6.12 and 6.14 will govern the payment of royalties from Isis to JBI under this Section 10.3.4(d)(ii), *mutatis mutandis*.

(iii) JBI will assign to Isis any Product-Specific Patent Rights and Isis' interest in any Jointly-Owned Program Patents that, in each case relate to the applicable Discontinued Product(s) previously assigned by Isis to JBI under this Agreement;

(iv) JBI 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 JBI 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 4.4;

(v) JBI 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 JBI have any obligation to license to Isis any trademarks used by JBI both in connection with the Product and in connection with the sale of any other product or service, including any JBI- or JBI-formative marks; and

(vi) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Pre-Clinical Development Program (or the corresponding Drug Discovery Program), and JBI will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in JBI'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 JBI of such intention at least 60 days before such Patent Right will become abandoned, and JBI 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.

(e) If Isis terminates this Agreement due to JBI's material breach or JBI terminates this Agreement for convenience, upon Isis' written request pursuant to a mutually agreed supply agreement, JBI will sell to Isis any bulk API, Clinical Supplies and Finished Drug Product in JBI's possession at the time of such termination, at a price equal to JBI's cost at the time of manufacture.

(f) To the extent requested by Isis, JBI will promptly assign to Isis any manufacturing agreements identified by Isis solely to the extent related to the applicable Discontinued Products to which JBI is a party.

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 JBI on July 30, 2014 (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 **Announcement of Transaction**. On or promptly after the Effective Date, the Parties will issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties and included in Schedule 11.4.

11.4.2 **Other Disclosures**. 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 a Drug Discovery Program, a Product, 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.

11.4.3 **Use of Name**. Except as set forth in Section 11.4.8, 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.

11.4.4 **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 JBI's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.5 **JBI Disclosures After Option Exercise**. After Option if JBI intends to make a press release or similar public communication disclosing regulatory discussions, the efficacy or safety data or results related to such Product or JBI's sales projections, (i) JBI 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) JBI will in good faith consider any changes that are timely recommended by Isis.

11.4.6 **Scientific or Clinical Presentations**. The Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of 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 Drug Discovery 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 **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.

11.4.8 **Acknowledgment**. JBI will acknowledge in any press release, public presentation or publication regarding the collaboration or a Product, Isis' role in discovering and developing the Product, that the Product is under license from Isis and otherwise acknowledge Isis' contributions, and Isis' stock ticker symbol (Nasdaq: ISIS). Isis may include the Product (and identify JBI as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1 **Dispute Resolution**.

12.1.1 **General.** The Parties recognize that a dispute may arise relating to this Agreement ("***Dispute***"). Except as set forth in Section 12.1.5 any Dispute, including Disputes that may involve the parent company, subsidiaries, or affiliates under common control of any Party, shall be resolved in accordance with this Section 12.

12.1.2 **Continuance of Rights and Obligations During Pendency of Dispute Resolution.** If there are any Disputes in connection with this Agreement, including Disputes related to termination of this Agreement under Section 10, all rights and obligations of the Parties shall continue until such time as any Dispute has been resolved in accordance with the provisions of this Section 12.

12.1.3 **Escalation**. Subject to Section 12.1.5, any claim, Dispute, or controversy as to the breach, enforcement, interpretation or validity of this Agreement will be referred to the Global Therapeutic Area Head, Immunology of JBI and the Chief Operating Officer of Isis (the "***Executives***") for attempted resolution. In the event the Executives are unable to resolve such Dispute within 30 days of such Dispute being referred to them, then, upon the written request of either Party to the other Party, the Dispute shall be subject to arbitration in accordance with Section 12.1.4, except as expressly set forth in Section 12.1.5 or Section 12.3.

12.1.4 Arbitration.

(a) If the Parties fail to resolve the Dispute through Escalation, and a Party desires to pursue resolution of the Dispute, the Dispute shall be submitted by either Party for resolution in arbitration pursuant to the then current CPR Non-Administered Arbitration Rules ("CPR Rules") (www.cpradr.org), except where they conflict with these provisions, in which case these provisions control. The arbitration will be held in Chicago, Illinois. All aspects of the arbitration shall be treated as confidential.

(b) The arbitrators will be chosen from the CPR Panel of Distinguished Neutrals, unless a candidate not on such panel is approved by both Parties. Each arbitrator shall be a lawyer with at least 15 years of experience with a law firm or corporate law department of over 25 lawyers or who was a judge of a court of general jurisdiction. To the extent that the Dispute requires special expertise, the Parties will so inform CPR prior to the beginning of the selection process.

(c) The arbitration tribunal shall consist of three arbitrators, of whom each Party shall designate one in accordance with the "screened" appointment procedure provided in CPR Rule 5.4. The chair will be chosen in accordance with CPR Rule 6.4.

(d) If, however, the aggregate award sought by the Parties is less than $5 million and equitable relief is not sought, a single arbitrator shall be chosen in accordance with the CPR Rules.

(e) Candidates for the arbitrator position(s) may be interviewed by representatives of the Parties in advance of their selection, provided that all Parties are represented.

(f) The Parties agree to select the arbitrator(s) within 45 days of initiation of the arbitration. The hearing will be concluded within nine (9) months after selection of the arbitrator(s) and the award will be rendered within 60 days of the conclusion of the hearing, or of any post hearing briefing, which briefing will be completed by both sides within 45 days after the conclusion of the hearing. In the event the Parties cannot agree upon a schedule, then the arbitrator(s) shall set the schedule following the time limits set forth above as closely as practical.

(g) The hearing will be concluded in ten hearing days or less. Multiple hearing days will be scheduled consecutively to the greatest extent possible. A transcript of the testimony adduced at the hearing shall be made and shall be made available to each Party.

(h) The arbitrator(s) shall be guided, but not bound, by the CPR Protocol on Disclosure of Documents and Presentation of Witnesses in Commercial Arbitration (www.cpradr.org) ("Protocol"). The Parties will attempt to agree on modes of document disclosure, electronic discovery, witness presentation, etc. within the parameters of the Protocol. If the Parties cannot agree on discovery and presentation issues, the arbitrator(s) shall decide on presentation modes and provide for discovery within the Protocol, understanding that the Parties contemplate reasonable discovery.

(i) The arbitrator(s) shall decide the merits of any Dispute in accordance with the law governing this Agreement, without application of any principle of conflict of laws that would result in reference to a different law. The arbitrator(s) may not apply principles such as "amiable compositeur" or "natural justice and equity."

(j) The arbitrator(s) are expressly empowered to decide dispositive motions in advance of any hearing and shall endeavor to decide such motions as would a United States District Court Judge sitting in the jurisdiction whose substantive law governs.

(k) The arbitrator(s) shall render a written opinion stating the reasons upon which the award is based. The Parties consent to the jurisdiction of the United States District Court for the district in which the arbitration is held for the enforcement of these provisions and the entry of judgment on any award rendered hereunder. Should such court for any reason lack jurisdiction, any court with jurisdiction may act in the same fashion.

(l) Each Party has the right to seek from the appropriate court provisional remedies such as attachment, preliminary injunction, replevin, etc. to avoid irreparable harm, maintain the status quo, or preserve the subject matter of the Dispute. Rule 14 of the CPR Rules does not apply to this Agreement.

(m) EXCEPT IN THE CASE OF COURT ACTIONS PERMITTED BY SECTION 12.1.5 AND FOR CLAIMS NOT SUBJECT TO ARBITRATION PURSUANT TO SECTION 12.1.4 AS SET FORTH IN SECTION 12.1.5, EACH PARTY HERETO WAIVES: (1) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY, (2) WITH THE EXCEPTION OF RELIEF MANDATED BY STATUTE, ANY CLAIM TO PUNITIVE, EXEMPLARY, MULTIPLIED, INDIRECT, CONSEQUENTIAL OR LOST PROFITS/REVENUES DAMAGES, AND (3) ANY CLAIM FOR ATTORNEY FEES, COSTS AND PREJUDGMENT INTEREST.

(n) Each Party will bear its own attorney's fees, costs, and disbursements arising out of the arbitration, and will pay an equal share of the fees and costs of the arbitrator; *provided, however,* the arbitrator will be authorized to determine whether a Party is the prevailing party, and if so, to award to that prevailing party reimbursement for any or all of its reasonable attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, *etc.*), and/or the fees and costs of the Administrator and the arbitrator.

12.1.5 **Injunctive Relief; Court Actions.** Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek from any court of competent jurisdiction, in addition to any other remedy it may have at law or in equity, injunctive or other equitable relief in the event of an actual or threatened breach of this Agreement by the other Party, without the posting of any bond or other security, and such an action may be filed and maintained notwithstanding any ongoing discussions between the Parties or any ongoing arbitration proceeding. The Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive or equitable relief would be appropriate remedy. 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 Patent Rights or other intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 12.1.4.

12.2 **Governing Law; Jurisdiction; Venue; Service of Process**. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of New York, U.S.A., without reference to conflicts of laws principles.

12.3 **Recovery of Losses**. 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 6.9.3(c)). Except for the offsets and credits explicitly set forth in Section 6.12, and Section 6.9.3(b) neither Party will have the right to set off 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 prior written consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that (i) Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without JBI's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction, and (ii) each Party may assign this Agreement and the rights, obligations and interests of such Party hereunder, without the other Party's consent to any Third Party 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 with a Third Party, provided that in the event of any such transaction (whether this Agreement is actually assigned or is assumed by the acquiring Third Party or the successor corporation (as applicable) by operation of law (*e.g.*, in the context of a reverse triangular merger)), intellectual property rights of the acquiring Third Party that existed prior to such transaction shall not be included in the technology licensed hereunder or otherwise subject to this Agreement; provided that if JBI transfers or assigns this Agreement to [***] described in this Agreement, then JBI (or such Affiliate), will [***] due Isis under ARTICLE 6 for the [***] (defined below) such that Isis receives [***].

The [***].

To the extent Isis utilizes [***] in any year, Isis will [***] to JBI [***]. To assist JBI in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which JBI [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Isis [***], Isis will provide JBI with Isis' Annual tax returns (federal and state) and, in years in which Isis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.4.1 **Termination of Reporting Obligations Upon Isis Change of Control**. If there is a change in control of Isis, JBI, at its discretion, may terminate all reporting obligations regarding the Development and/or Commercialization of any Products including reporting under the Information Sharing Committee, except in all cases JBI will continue to provide the reports, audit rights and other information required under Sections 6.10, 6.11, 6.12 and 6.13.

12.5 **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.

12.6 **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 JBI, addressed to:

Janssen Research & Development, LLC
Murray McKinnon, PhD1400 McKean Road
Spring House, PA 19477
Mmckinno2@its.jnj.com

with a copy to:

Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Attn: Brian Carey
Bcarey2@its.jnj.com

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.

12.7 **ISIS Reporting of This Agreement**. Isis shall provide JBI with at least [***] ([***]) days written notice of any disclosure of this document to a Third Party or to a governmental authority. The Parties agree to promptly convene to discuss such disclosure and discuss, *inter alia,* the subject matter that may be redacted prior to such submission. Notwithstanding the foregoing, Isis may (i) disclose this Agreement to Isis' legal counsel, auditors, and other professional advisors on a need-to-know basis, in each case where such advisors have agreed to confidentiality provisions no less restrictive than those of this Agreement, and (ii) may disclose the publicly available redacted version of this Agreement once such redacted version has been filed publicly with the SEC.

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 identifying the Licensed Technology 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.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

JANSSEN BIOTECH INC.

By: /s/ John Wilson
Name: John Wilson
Title: Vice President, Janssen Biotech Inc.

List of Appendices and Schedules

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***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 JBI 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 JBI 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***" means Third Party intellectual property that is necessary to [***]*; provided* Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***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 1.6.5.

"***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 GMP (unless expressly stated otherwise) 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 JBI (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 or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and is designed to hybridize to a nucleic acid transcript via the binding, partially or wholly, of such compound to the nucleic acid transcript.

"***Audit Report***" has the meaning set forth in Section 6.12.

"Autoimmune Diseases" is any of a number of diseases characterized by abnormal functioning of the immune system which causes the immune system to attack the body's own tissues. Crohn's disease and ulcerative Colitis which are inflammatory bowel diseases are included as autoimmune diseases for purposes of this Agreement.

"***Bankruptcy Code***" has the meaning set forth in Section 7.12.

"***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 financial quarter based on the J&J Universal Calendar for that year (a copy of which is attached hereto as APPENDIX 3) and is used for JBI's internal and external reporting purposes; provided, however, that the first Calendar Quarter for the first Calendar Year extends from the Effective Date to the end of the then current Calendar Quarter and the last Calendar Quarter extends from the first day of such Calendar Quarter until the effective date of the termination or expiration of the Agreement.

"***Calendar Year***" means a year based on the J&J Universal Calendar for that year. The Last Calendar Year of the Term begins on the first day of the J&J Universal Calendar Year for the year during which termination or expiration of the Agreement will occur, and the last day of such Calendar Year will be the effective date of such termination or expiration.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase I Clinical Trial, Phase II Clinical Trial, Phase III Clinical Trial or Phase IV Clinical 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 Target***" means a gene target designated as a Collaboration Target pursuant to Section 1.2.

"***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) JBI, with respect to a Product that is being Developed and Commercialized by or on behalf of JBI, 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 JBI's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the "*General Activities*" described in SCHEDULE 5.2, 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 Drug Discovery Plan and Development Plan.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Completion of PoC***" means, on a Product-by-Product basis, when JBI receives the primary end-point data generated under the statistical analysis plan of the first PoC Study.

"***Compound***" means on a Drug Discovery Program-by-Drug Discovery 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 Drug Discovery Plan, including each Development Candidate under such Drug Discovery 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.

"***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 JBI Supported Pass-Through Costs in the case of JBI), 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 a license under such patent, the act of making, using or selling 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 5.4.1.

"Currency Hedge Rate(s)" is calculated as a weighted average hedge rate of the outstanding external foreign currency forward hedge contract(s) of Johnson & Johnson's Global Treasury Services Center (GTSC) and its Affiliates with third party banks. The hedge contract(s) is entered into to protect the transactional foreign exchange risk exposures of JBI by reducing the impact of foreign currency volatility through a systematic buildup of a yearly Currency Hedge Rate(s).

"***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' Research Management Committee in accordance with Isis' standard procedures for designating development candidates (and giving good faith consideration to the input of JBI's representatives on the JRC) 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 Development Candidate: [***].

"***Development Plan***" has the meaning set forth in Section 1.3.2(b).

"***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 Rejection Condition" has the meaning set forth in Section 1.2.3.

"***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.

"***Drug Discovery Plan***" has the meaning set forth in Section 1.3.2(b).

"***Drug Discovery Program***" has the meaning set forth in Section 1.2.

"***Drug Discovery Term***" has the meaning set forth in Section 1.5.1.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***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 JBI, 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 JBI.

"***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 a given Calendar Year the rate that Isis charges for a full time equivalent [***].

"Fully Absorbed Cost of Goods" means the reasonable and necessary internal and third party costs with no mark-up incurred by Isis in making or acquiring of product as determined using the methodology set forth in SCHEDULE 4.4.4 fairly applied and as employed on a consistent basis throughout Isis' operations and shall not include inter-company profits among Isis and its Affiliates. .

"***GCP***" means the then current standards for clinical trials for pharmaceuticals, as set forth in the United States Code of Federal Regulations, ICH guidelines and applicable regulations, laws or rules as promulgated thereunder.

"***Generic Product***" means, with respect to a particular Product in a country, a generic or biosimilar pharmaceutical product, that is not produced, licensed or owned by JBI or any of its Affiliates, that:(a) contains the same, or a bioequivalent of the, active ingredient as a Product; and (b) is approved for use in such country by a regulatory authority through a regulatory pathway by referencing clinical data first submitted for obtaining regulatory approval for such Product. Generic Product includes any pharmaceutical products obtained via a bioequivalence or bioavailability showing such as those covered by section 505(b)(2) or under 505(j) of the U.S. Federal Food, Drug, and Cosmetic Act or an equivalent outside the United States.

"***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.

"***GMP***" 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.

"[***].

"***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. IND-Enabling Toxicology Studies do not include chronic toxicology studies or reproductive toxicology studies.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Indication***" means distinct, well-categorized disease or condition in humans for which a separate marketing authorization (or amendment to a marketing authorization) is required.

"***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 5.3.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***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 8.2.2(a) attached hereto.

"***Isis Formulation Patents***" means the Patent Rights listed on Schedule 8.2.2(d) attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.9.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.6.

"***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 8.2.2(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 8.2.2.

"***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 SCHEDULE 8.2.2(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 [***].

"***JBI***" has the meaning set forth in the Preamble of this Agreement.

"***JBI Royalty***" has the meaning set forth in Section 6.8.1.

"***JBI Know-How***" means any Know-How owned, used, developed by, or licensed to JBI or its Affiliates, in each case to the extent Controlled by JBI or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the JBI Program Know-How.

"***JBI Patents***" means any Patent Rights included in the JBI Technology.

"***JBI Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to JBI or its Affiliates, in each case to the extent Controlled by JBI or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***JBI Program Know-How***" has the meaning set forth in Section 7.1.2.

"***JBI Program Patents***" has the meaning set forth in Section 7.1.2.

"***JBI Program Technology***" has the meaning set forth in Section 7.1.2.

"***JBI-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***JBI Supported Pass-Through Costs***" means [***].

"***JBI Technology***" means the JBI Program Technology, Jointly-Owned Program Technology, JBI Product-Specific Patents and any trademarks described in Section 4.1.5, owned, used, developed by, or licensed to JBI or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***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 including pricing.

"***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.

"***JRC***" has the meaning set forth in Section 1.6.1.

"***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, and in each case that are unpatented.

"***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 delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, Isis Formulation 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 (excluding Phase IV Clinical Trials) 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 including pricing.

"***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 amounts invoiced on sales of a Product by JBI or any of its Affiliates or sublicensees to a Third Party purchaser in an arms-length transaction, less the following customary deductions, determined in accordance with US generally accepted accounting principles and standard internal policies and procedures and accounting standards consistently applied throughout Johnson & Johnson, to the extent specifically and solely allocated to such Product and actually taken, paid, accrued, allowed, included or allocated based on good faith estimates in the gross sales prices with respect to such sales (and consistently applied as set forth below):

a) normal and customary trade, cash and/or quantity discounts, allowances, and credits allowed or paid, in the form of deductions actually allowed or fees actually paid with respect to sales of such Product (to the extent not already reflected in the amount invoiced) excluding commissions for commercialization;

b) excise taxes, use taxes, tariffs, sales taxes and customs duties, and/or other government charges imposed on the sale of Product to the extent included in the price and separately itemized on the invoice price (but specifically excluding, for clarity, any income taxes assessed against the income arising from such sale) (including VAT, but only to the extent that such VAT taxes are not reimbursable or refundable);
c) outbound freight, shipment and insurance costs to the extent included in the price and separately itemized on the invoice price;
d) compulsory payments and cash rebates related to the sales of such Product paid to a Governmental Authority (or agent thereof) pursuant to governmental regulations by reason of any national or local health insurance program or similar program, to the extent allowed and taken; including Government levied fees as a result of Healthcare Reform policies
e) retroactive price reductions, credits or allowances actually granted upon rejections or returns of Product, including for recalls or damaged good and billing errors; and
f) rebates, chargebacks, and discounts (or equivalent thereof) actually granted to managed health care organizations, pharmacy benefit managers (or equivalent thereof), federal, state/provincial, local or other governments, or their agencies or purchasers, reimbursers, or trade customers.

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.

All aforementioned deductions shall only be allowable to the extent they are commercially reasonable and shall be determined, on a country-by-country basis, as incurred in the ordinary course of business in type and amount consistent with the Party's, the Affiliate's, or Third Party sublicensee's (as the case may be) business practices consistently applied across its product lines and accounting standards and verifiable based on the Johnson & Johnson sales reporting system. All such discounts, allowances, credits, rebates, and other deductions shall be fairly and equitably allocated to Product and other products of the Party and its Affiliates and sublicensees such that Product does not bear a disproportionate portion of such deductions.

<u>The following shall be excluded for the purposes of calculating royalties or sales milestones:</u>
a) Sales of Product by and between JBI and its Affiliates and sublicenses so long as such Product is subsequently resold to a Third-party end user where such resale to such Third-party end user is included in Net Sales
b) Sales of Product for the use in conducting clinical trials, pre-clinical studies or other research or development activities in a country in order to obtain Regulatory Approval of Product in such country
c) Product provided free of charge for a *bona fide* charitable purpose

d) Product used for commercially reasonable free sampling programs.
e) Sales of Product free of charge for Compassionate
f) Sales of Product for Named Patient Sales where such Product is sold at a significant discount to the proposed price for the Product following Approval.

In the event Product(s) are sold in combination with other products or services from JBI, its Affiliates or sublicensees and the customer receives a specific discount for such "bundling" of products (for clarity, this situation describes bundling of two or more separate products, each in finished dosage form, and not a fixed combination of two active pharmaceutical ingredients), the Net Sales of the said Product(s), for the purposes of determining royalty payments, shall be determined by multiplying the relevant Net Sales by the fraction, A/(A+B) where A is the weighted (by sales volume) average sale price in a particular country of the Product(s) in the previous Calendar Year when sold separately and B is the weighted average sale price in that country in the previous Calendar Year of the other product sold separately. In the event that such average sale price cannot be determined for either of the Product(s) or the other product(s) it has been sold with, in combination, then for purposes of determining the royalty payments, JBI will propose a reasonable good faith estimate of the fair market value of each component (and JBI will provide Isis a justification and support for such estimates) which will be substituted for the weighted average sales price for each such product in the formula above. If JBI, 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.

"***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.

"***Option***" has the meaning set forth in Section 3.1.

"***Option Deadline***" has the meaning set forth in Section 3.1.

"***Option Period***" means, with respect to a Drug Discovery Program, the period beginning on the date when the applicable Collaboration Target was designated and ending on the expiration or earlier termination of the Option with respect to such Drug Discovery Program.

"***Out-of-Pocket Expenses***" means the amounts paid to Third Party vendors or contractors, for services or materials provided by them directly in the performance of activities to the extent such services or materials apply directly to the activities under this agreement.

"***Party***" or "***Parties***" means JBI 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, collaboration or sponsored research 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.

"***Phase I Clinical Trial***" means a human clinical trial that is intended to initially evaluate the safety, metabolism and pharmacokinetics of a therapeutic agent that would otherwise satisfy the requirements of 21 C.F.R. 312.21(a) or an equivalent clinical trial in a country in the Territory other than the United States.

"***Phase II Clinical Trial***" means a human clinical trial, for which the primary endpoints include a determination of safety, dose ranges or an indication of efficacy of a therapeutic in patients being studied as described in 21 C.F.R. §312.21(b), or an equivalent clinical trial in a country in the Territory other than the United States, and that is prospectively designed to generate sufficient data (if successful) to commence pivotal clinical trials.

"***Phase III Clinical Trial***" means a human clinical trial (regardless of whether actually designated as "Phase III") that is prospectively designed, along with other Phase III Clinical Trials, to demonstrate statistically whether a therapeutic is safe and effective for use in humans in the indication being investigated as described in 21 C.F.R. §312.21(c), or an equivalent clinical trial in a country in the Territory other than the United States.

"***Phase IV Clinical 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.

"***Plan***" means a Drug Discovery Plan and/or Development Plan, as applicable.

"PoC Study" means a study conducted during a Phase II Clinical Trial designed to give preliminary evidence of efficacy and safety for a Product.

"***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 8.2.2(e) attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, on a Drug Discovery Program-by-Drug Discovery Program basis, a finished drug product containing a unique and specific Compound as an active pharmaceutical ingredient. Each Product shall contain a different specific Compound (s).

"***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.

"***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.

"***Research***" means conducting the research activities with Compounds as set forth in each Drug Discovery 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.

"***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 Period***" has the meaning set forth in Section 6.8.2(a).

"***Sales Milestone Event***" has the meaning provided in Section 6.7.

"[[***].

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.2.

"***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 JBI Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Substitution Fee"*** means $[***] per substituted target to be paid by JBI following Isis' acceptance of JBI's proposed substitute gene target under Section 1.2.5**.**

"***Supplemental Information***" has the meaning provided in Section 1.3.5.

"***Target Nomination Period***" has the meaning set forth in Section 1.2.1.

[***]

"***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.

"***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 six years, not including in calculating such six-year period 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 six 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

[***]

APPENDIX 3

J&J Universal Calendar

2015 UNIVERSAL CALENDAR

	M	T	W	T	F	S	S
	29	30	31				
JAN				1	2	3	4
(4 Weeks)	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
FEB							1
(4 Weeks)	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	
							1
MAR	2	3	4	5	6	7	8
(5 Weeks)	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31					
APR			1	2	3	4	5
(4 Weeks)	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30			
MAY					1	2	3
(4 Weeks)	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
JUN	1	2	3	4	5	6	7
(5 Weeks)	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28

	M	T	W	T	F	S	S
	29	30					
JUL			1	2	3	4	5
(4 Weeks)	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	31		
AUG						1	2
(4 Weeks)	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
	31						
SEP		1	2	3	4	5	6
(5 Weeks)	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30				
OCT				1	2	3	4
(4 Weeks)	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
NOV							1
(4 Weeks)	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30						
DEC		1	2	3	4	5	6
(6 Weeks)	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30	31			
					1	2	3

SCHEDULE 1.6.1

JRC GOVERNANCE

(a) The JRC will determine the JRC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JRC will codify these operating procedures in the written minutes of the first meeting.

(b) The JRC may hold meetings in person or by audio or video conference as determined by the JRC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at JBI's facilities in the U.S.). Alliance Managers will attend JRC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JRC 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 JRC meetings occur, JRC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.6.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The JRC members from the same Party will collectively have one vote. The JRC will strive to make recommendations with approval of both Isis members and JBI members, and record such recommendations in the minutes of the applicable JRC meeting.

(e) The JRC 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 JRC dissolves.

SCHEDULE 1.6.5

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 Drug Discovery Programs;

(c) Organizing JRC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JRC 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 JRC;

(f) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.6;

(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 JBI, to assist JBI in understanding and complying with the contractual obligations under the Isis In-License Agreements after Option exercise.

SCHEDULE 4.4.4

Isis' Fully Absorbed Cost of Goods Methodology

[***]

SCHEDULE 5.2

JBI's Development and Commercialization Activities

[***]

SCHEDULE 6.9.1

Certain Isis In-License Agreements

(Relevant to the Drug Discovery Programs as of the Effective Date)

[***]

SCHEDULE 8.2.2(a)

Isis Core Technology Patents

[***]

SCHEDULE 8.2.2(b)

Isis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.2(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.2(d)

Isis Formulation Patents

[***]

SCHEDULE 8.2.2(E)

Prior Agreements

[***]

Schedule 11.4 – Press Release

ISIS PHARMACEUTICALS ANNOUNCES COLLABORATION WITH JANSSEN TO DISCOVER AND DEVELOP RNA-TARGETED THERAPEUTICS FOR AUTOIMMUNE DISEASES IN THE GI TRACT

-- Collaboration Combines Isis' RNA-Targeted Technology with Expertise of Janssen in Autoimmune Disorders and Therapeutic Formulation --

Carlsbad, Calif., Jan. [5], 2015 –Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today announced that the company has entered into a global collaboration with Janssen Biotech, Inc. (Janssen) to discover and develop antisense drugs to treat autoimmune disorders of the gastrointestinal (GI) tract. The collaboration brings together Isis' RNA-targeted technology platform and the expertise of Janssen in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders in the GI tract.

"We are excited to be working with Janssen to apply our drug discovery and development efforts in this therapeutic area. This collaboration broadens the utility of our drug discovery technology to new targets in the GI tract and expands the administration of antisense drugs to local delivery, including oral delivery, to the gut," said B. Lynne Parshall, chief operating officer at Isis Pharmaceuticals. "We are the leader in RNA-targeted therapeutics and our innovation and the successes of our pipeline drugs enable us to form collaborations, like this one, with leaders in specific therapeutic areas. This partnering strategy ensures that we have access to resources that support and enhance our drug discovery efforts and also provides us with collaborators, like Janssen, who are uniquely capable of conducting development, marketing and commercial efforts for these drugs. ."

Under the terms of the agreement, which covers three programs, Isis will receive $35 million in upfront payments, including a payment to initiate human lead optimization on the first collaboration target. Isis is eligible to receive nearly $800 million in development, regulatory and sales milestone payments and license fees for these programs. In addition, Isis will receive tiered royalties that on average are double-digits on sales from any product that is successfully commercialized. Janssen has the option to license a drug from each of the programs once a development candidate is identified. If Janssen exercises its option, it will assume global development, regulatory and commercialization responsibilities.

ABOUT ISIS PHARMACEUTICALS, INC.
Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 34 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include a ISIS-APOCIII$_{Rx}$, a drug Isis is developing to treat patients with severely high triglycerides, such as patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' alliance with Janssen, Isis' research, development and commercial opportunities in developing antisense drugs to treat inflammatory bowel disease. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs 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. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

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

Isis Pharmaceuticals' Contacts:

D. Wade Walke, Ph.D.
Vice President, Corporate Communications and Investor Relations
760-603-2741

Amy Blackley, Ph.D.
Associate Director, Corporate Communications
760-603-2772

###

EXHIBIT 10.61

Execution Copy

AMENDMENT NO.2

This Amendment No.2 ("the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at 151 85 Södertälje, Sweden and with offices at SE-43 183 Mölndal, Sweden ("AstraZeneca")
(2) ISIS PHARMACEUTICALS, INC., a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Isis")

and is made effective as of the 15th day of October, 2014 (the "Amendment Effective Date")

Recitals

WHEREAS, the Parties desire to further amend, modify and restate certain terms and conditions of the Agreement.

Agreement

NOW, THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

1. Definitions
Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. Modifications
Article 8.4, Table 1, shall be deleted and replaced by the following:

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
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]

3. Amendment Effective Date

This Amendment shall become effective on the Amendment Effective Date.

4. Entire Agreement

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreeement. The Agreeemnt together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreeemnet, as amended. Each Party confirms that it is not relying on any representations, warranties or covenants of the other Party except as specifically set out in the Agreement as amended. Nothing in this Agreement is intended to limit or exclude any liability or fraud. All Schedules referred to in this Amendment are intended to be and are hereby specifically incorporated into and made a part of the Agreement. The Parties hereby agree that subject to the modifciations specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

Execution

THIS AGREEMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB		**ISIS Pharmaceuticals, INC**	
Signature :	*/s/ M. Schindler*	Signature :	*/s/ B. Lynne Parshall*
Name :	M. Schindler	Name :	B. Lynne Parshall
Title :	16 10 14	Title :	Chief Operating Officer

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

Akcea Therapeutics, 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, 333-188407 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, 333-190408) of Isis Pharmaceuticals, Inc. and in the related Prospectus of our reports dated February 27, 2015, 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, 2014.

/s/ ERNST & YOUNG LLP

San Diego, California
February 27, 2015

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 27, 2015

/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 27, 2015

/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 year ended December 31, 2014, 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 27, 2015

/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.