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, 2009

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.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

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

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

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $.001 Par Value

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

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

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

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

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

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Select Market was $1,361,263,134 as of June 30, 2009.*

The number of shares of voting common stock outstanding as of February 22, 2010 was 99,063,964.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement for the fiscal year ended December 31, 2009 to be filed on or about April 16, 2010 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 2, 2010 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 68 to 72 incorporates several documents by reference as indicated therein.

* Excludes 15,657,564 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, 2009. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. and Regulus Therapeutics, our majority-owned subsidiary. 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 products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

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

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

Ibis T5000™ is a trademark of Ibis Biosciences, Inc.

Vitravene® is a registered trademark of Novartis AG.

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 is included on or linked to our Internet site is not a part of this report or any registration statement that incorporates this report by reference. Our filings may also be read and copied at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

PART I

Item 1. Business

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Bristol-Myers Squibb, Genzyme Corporation and Eli Lilly and Company. Additionally, we have created a consortium of smaller companies that can broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core

areas of focus through collaborations with Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc., a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen, Inc. and Archemix Corp. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as Ibis Biosciences, Inc., a subsidiary of ours that we sold in early 2009 to Abbott Molecular Inc., or AMI, a wholly owned subsidiary of Abbott Laboratories. All of these aspects fit into our unique business model and create continued shareholder value.

Through the power and efficiency of our technology, we can continuously add new antisense drugs to our development pipeline each year. For example, in 2009, we added three new drugs to our internal development pipeline, and we anticipate continuing to grow this pipeline at a rate of three to five new drugs per year. Because we can discover more drugs and drug candidates than we can develop ourselves, our partnership strategy is important as it allows us to focus on our key therapeutic franchises while also creating an expansive pipeline with multiple partnerships. We focus our research and development efforts primarily in cardiovascular, metabolic and neurodegenerative diseases and cancer while our partners are developing antisense drugs in these and other areas, including inflammatory disease.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. Our clinical experience with mipomersen demonstrates that antisense drugs work in man. We and Genzyme reported positive data from two Phase 3 studies in patients with familial hypercholesterolemia, or FH. Both studies met their primary and secondary endpoints with reductions in LDL-cholesterol, or LDL-C,

and other generally accepted risk factors for cardiovascular disease. These data are consistent with our observations of mipomersen in earlier clinical studies and support the profile of the drug as a novel treatment to reduce LDL-C in patients with high cholesterol, and at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform and increased the value of our drugs.

In addition to mipomersen, many of the other drugs in our pipeline are demonstrating encouraging therapeutic activity in a variety of diseases. We reported positive Phase 2 data from our protein tyrosine phosphatase 1B, or PTP-1B, drug showing consistent and statistically significant reductions in short and intermediate measures of glucose control, reductions in LDL-C and a tendency toward weight loss. We believe these parameters added together create an encouraging profile for a new therapy to treat type 2 diabetics. We also reported positive Phase 1 data on our glucagon receptor, or GCGR, inhibitor, one of four programs in our metabolic disease franchise. Our partnered drugs are also showing encouraging activity in numerous diseases. For example, our partner OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc., reported Phase 2 data showing that OGX-011, an antisense drug we and OncoGenex co-discovered, provides survival advantage in patients with prostate cancer compared to standard therapies, and our partner Altair Therapeutics Inc. reported positive Phase 1 data on AIR645, our first inhaled antisense drug in clinical development for the treatment of asthma. These data highlight the broad therapeutic activity of antisense drugs and the power of our antisense technology platform to generate drugs that address significant medical needs.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Since 2007, our partnerships have generated an aggregate of more than $750 million in payments from licensing fees, equity purchase payments and milestone payments. In addition, for our partnered drugs we have the potential to earn approximately $2.5 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Beyond drug development, we create significant shareholder value through products of our inventions that other companies are developing and commercializing. For example, Ibis was a product of our innovative technology with applications in a number of areas, including infectious disease detection in hospital and clinical settings. In early 2009, we completed the sale of Ibis to AMI for a total purchase price of $215 million. We will continue to benefit from the success of Ibis through earn out payments from the sales of Ibis commercial products. This transaction represented a significant valuation for Ibis and a reflection of the value we created through our Ibis business.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements.

Below is a list of some of our key accomplishments for 2009 and early 2010.

2009 and Early 2010 Business Highlights

Drug Development Highlights

- Mipomersen continues to advance in clinical development and move closer to the market for patients who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. We and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with FH.
  - In a Phase 3 study evaluating mipomersen in patients with homozygous FH, we and Genzyme reported that the study met its primary endpoint with a 25% reduction in LDL-C after 26 weeks of treatment, compared to a decrease of 3% for placebo ($p<0.001$), which constitutes an average reduction of LDC-C greater than 100 mg/dL, and also met all of its secondary and tertiary endpoints.
  - In a Phase 3 study evaluating mipomersen in patients with heterozygous FH, we and Genzyme reported that the study met its primary endpoint with a 28% reduction in LDL-C after 26 weeks of treatment, compared to an increase of 5% for placebo ($p<0.001$) and also met all of its secondary endpoints. Patients treated with mipomersen had an average LDL-C of 104 mg/dL at the end of the study and 45% of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL.
- We reported positive Phase 2 data on ISIS 113715 in patients with type 2 diabetes on stable doses of sulfonylurea.
  - In this study, patients treated with 200 mg per week of ISIS 113715 for 13 weeks achieved consistent and statistically significant reductions in multiple short and intermediate measures of glucose control.
- We reported positive Phase 1 data in which ISIS-GCGR$_{Rx}$ produced a significant improvement in glucagon-induced blood glucose levels and was well tolerated.
- In addition, we and our partners continued to advance the drugs in our pipeline and reported encouraging clinical results in a broad range of diseases.
  - We and our partners presented positive Phase 1 data on six drugs including, LY2181308, OGX-427, ISIS-GCGR$_{Rx}$, AIR645, iCo-007 and ACHN-490, and positive Phase 2 data on OGX-011.
- We and our partners added four new drugs to our pipeline, including ISIS-FXI$_{Rx}$ to treat thrombosis, ISIS-SMN$_{Rx}$ to treat spinal muscular atrophy, or SMA, ISIS-APOCIII$_{Rx}$ to treat cardiovascular disease, and ACHN-490 to treat severe bacterial infections.
- We and our partners initiated Phase 1 clinical studies on four drugs and initiated Phase 2 studies on two drugs including AIR645 and EXC 001.

Corporate Highlights

- We executed our business strategy by successfully monetizing a key asset.
  - We sold our Ibis subsidiary to AMI.
- We benefited financially as our partners advanced drugs in development.
  - We received $11 million in milestone payments and sublicensing fees.
- We also benefited from our partnerships focused on developing and advancing certain RNA-based therapeutic technologies, receiving nearly $13 million in total.
- We supported our satellite company partners who are developing antisense drugs discovered by us for the treatment of a broad range of diseases by participating in the financings of Regulus, Altair, iCo Therapeutics Inc., and Excaliard Pharmaceuticals, Inc.

- We strengthened our intellectual property assets by obtaining patent grants and allowances that expand our fundamental patents and increase protection of our drugs in development.
- We also exclusively licensed certain intellectual property from the University of Massachusetts to develop drugs to treat SMA. Funding support for the University of Massachusetts' research program responsible for creating this intellectual property was provided in part by Families of SMA.
- Regulus formed a new alliance with GlaxoSmithKline, or GSK, to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for hepatitis C viral infection.

Drug Discovery and Development

Introduction to Drug Discovery

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

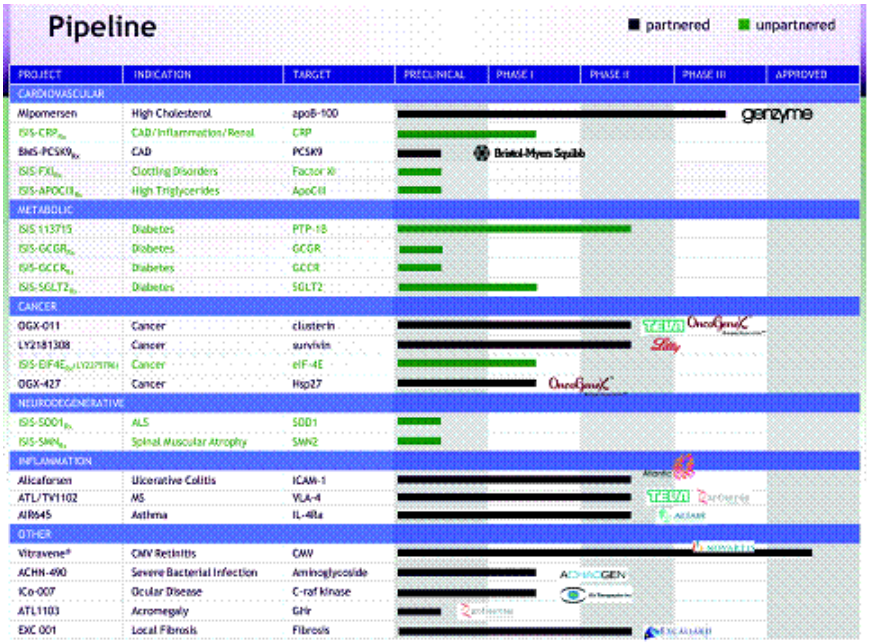
Our Development Projects

We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets we can build a large and diverse portfolio of drugs designed to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We also continue to improve our scientific understanding of our drugs and other disease targets, including the biological processes our disease targets use and the impact of our drugs on these processes.

With our expertise in discovering and characterizing novel antisense inhibitors, our scientists can optimize the properties of our antisense drugs for use with particular targets. Our scientists have made significant advances in chemistries, which we call our second-generation antisense drugs. Second-generation antisense drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. Our scientists have utilized our chemistry advancements to expand the therapeutic and commercial opportunities of our pipeline. These advancements along with shared manufacturing and analytical processes, shorten our timeline from initial concept to the first human dose.

We and our partners are developing antisense drugs for systemic, local and inhaled delivery. We expect to continue to bring new drugs into our pipeline, creating opportunities for future licensing transactions, and building a broad proprietary portfolio of drugs that are applicable to many disease targets.

The following table lists our approved product and each of our and our partners' drug development projects, their targets, disease indications and the development status of each. Prior to Phase 2 studies, we identify our drugs by the party responsible for development and the target, such as BMS-PCSK9$_{Rx}$ or ISIS-SGLT2$_{Rx}$, except when our partners refer to a drug by the partner's own compound number, such as AIR645 or EXC 001. As our drugs 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.



Cardiovascular Franchise

Cardiovascular disease is the leading cause of death in the United States. A common cause of cardiovascular disease is atherosclerosis, or hardening of the arteries, that occurs when cholesterol and inflammatory cells accumulate in blood vessels. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Lowering cholesterol is a key component in preventing and managing cardiovascular disease. Another independent risk factor for cardiovascular disease is high levels of C-reactive protein, or CRP, which clinicians associate with significantly worse outcomes in patients with cardiovascular disease.

Mipomersen — Mipomersen is a first-in-class apolipoprotein B, or apoB, synthesis inhibitor, or ABSI, currently in Phase 3 development as a potential novel treatment to reduce LDL-C in patients with high cholesterol and who are at high cardiovascular risk. Mipomersen is a second-generation antisense drug administered to patients through a once-weekly subcutaneous injection. It acts by decreasing the production of apoB, which provides the structural core for all atherogenic lipids, including LDL-C, which carry cholesterol through the bloodstream. In June 2008, we licensed mipomersen to Genzyme as part of a strategic transaction to develop and commercialize mipomersen.

In February 2010, we and Genzyme reported positive top-line data from our second Phase 3 trial evaluating mipomersen in patients with heterozygous FH. This is the second study to report from our broad Phase 3 program, and we expect the study to support the first regulatory filings in the U.S. and E.U. These two filings may also include patients with severe hypercholesterolemia.

About FH — FH is a genetic disorder in which patients cannot properly metabolize LDL-C, resulting in elevated LDL-C levels. FH patients experience a markedly increased risk of premature cardiovascular disease. There are two forms of FH: homozygous FH, where the patient inherits the same defective gene from both parents, and heterozygous FH where the patient inherits the defective gene from only one parent, thereby preserving some normal gene function. The homozygous form of FH is a very rare condition estimated to affect approximately one in a million people. Homozygous FH patients can have LDL-C levels greater than 600 mg/dL and are at very high risk for early coronary events and sudden death. Because many patients are resistant to the lipid-lowering effects of currently available therapies, it is difficult to effectively treat homozygous FH patients. Heterozygous FH is a more common form of the disorder, with a prevalence of approximately one in 500, and results in untreated LDL-C levels of approximately 300 mg/dL, double those of the general population.

Mipomersen Development — Mipomersen is intended to reduce LDL-C by preventing the formation of lipids that are responsible for the buildup of plaque in the arteries. The current recommendations for LDL-C goals from the National Cholesterol Education Program's Adult Treatment Panel III are less than 100 mg/dL for patients with very high cardiovascular risk and less than 130 mg/dL for patients with moderate cardiovascular risk. We and Genzyme are developing mipomersen for patients whose LDL-C levels exceed these recommendations despite taking maximally tolerated lipid-lowering treatments.

In Phase 2 studies, we evaluated mipomersen in multiple patient populations and as a single-agent and in combination with other lipid-lowering therapies. We reported data showing that mipomersen lowered LDL-C in all patient populations tested. Mipomersen lowered LDL-C when used either as a single agent or in combination with other lipid-lowering medicines. In addition, mipomersen lowered serum apoB, non-high-density lipoprotein-cholesterol, or non-HDL-C, triglycerides and lipoprotein (a), or Lp(a), all generally accepted risk factors for cardiovascular disease.

In November 2009, we and Genzyme reported positive data from a Phase 3 trial evaluating mipomersen in patients with homozygous FH. We designed the Phase 3 study in homozygous FH patients to test the efficacy and safety of adding mipomersen to substantial lipid-lowering therapy. The Phase 3 trial was a randomized, double-blind, placebo-controlled study that enrolled 51 homozygous FH patients and is one of the largest trials to date in this rare patient population. Patients were randomized 2:1 to receive a 200 mg dose of mipomersen or placebo by weekly injections for 26 weeks. The trial was conducted at 10 sites in seven countries in North America, Europe, Asia, South America and Africa.

We and Genzyme reported that the trial met its primary endpoint in an intent-to-treat analysis with a 25 percent reduction in LDL-C after 26 weeks of treatment, vs. 3 percent for placebo ($p < 0.001$), which constitutes an average reduction of LDL-C greater than 100mg/dL. The study also met all of its secondary and tertiary endpoints, suggesting that mipomersen may offer potential benefits beyond LDL-C reduction. Patients treated with mipomersen experienced a 27 percent reduction in apoB vs. 3 percent for placebo; a 21 percent reduction in total cholesterol vs. 2 percent for placebo; and a 25 percent reduction in non-HDL cholesterol vs. 3 percent for placebo (all $p<0.001$). Reductions were observed in other atherogenic lipids, including Lp(a) by 31 percent and VLDL-C by 17 percent (both $p<0.01$ vs. placebo); and triglycerides by 18 percent ($p=0.013$ vs. placebo). Mipomersen patients' HDL-C levels increased 15 percent ($p=0.035$ vs. placebo), which combined with the LDL-C reductions observed, resulted in improved LDL/HDL ratios, a ratio considered an important measure of cardiovascular risk. Mipomersen patients' LDL/HDL ratios decreased by 34 percent ($p<0.001$ vs. placebo). Although the patients were on maximally tolerated statins and other lipid-lowering therapies, their average LDL-C at baseline was greater than 400 mg/dL, confirming that the population is one in which LDL-C reduction is challenging to achieve. The reductions observed in the study were in addition to those achieved with the patients' existing therapeutic regimen.

Of the 34 patients treated with mipomersen, 28 completed the study. Of the six discontinuations, one patient discontinued due to elevations in liver transaminases that did not represent a Hy's Law case, an indicator of drug-induced liver injury, and was not associated with any other signs of liver toxicity. Of the remaining discontinuations, two patients stopped treatment due to injection site reactions, one patient stopped treatment due to a rash, one patient stopped treatment for personal reasons and one patient was discontinued due to patient non-compliance. Consistent with previous studies evaluating mipomersen, the most commonly observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases. Four patients had elevations in liver transaminases above 3 x ULN, or three times the upper limit of normal, three of whom reached between 5 and 8 x ULN. None of these patients, including the patient who discontinued the study, had changes in other laboratory tests to indicate liver dysfunction. In all cases, transaminases returned to entry criteria by the end of planned clinical observations.

In February 2010, we and Genzyme reported positive top-line data from a second Phase 3 study that evaluated mipomersen in patients with heterozygous FH. This study met its primary endpoint, with a highly statistically significant 28 percent reduction in LDL-C, after 26 weeks of treatment, compared with an increase of 5 percent for placebo ($p<0.001$). This study also met each of its secondary endpoints of reduction in apoB, total cholesterol and non-HDL cholesterol. Consistent with our previous studies evaluating mipomersen, the most commonly observed adverse events were injection site reactions and flu-like symptoms.

The study was a randomized, double-blind, placebo-controlled trial that enrolled 124 heFH patients, aged 18 and older with LDL-C levels greater than 100 mg/dL. Patients were randomized 2:1 to receive a 200 mg dose of mipomersen or placebo weekly for 26 weeks. All of the 124 patients in the study had pre-existing coronary artery disease, were taking a maximally tolerated dose of a statin and in many cases additional lipid-lowering drugs. Patients' average LDL-C at baseline was 150 mg/dL. Patients treated with mipomersen had an average LDL-C level of 104 mg/dL at the end of the study. Forty-five

percent of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL, a recognized treatment goal for high-risk patients. The reductions observed in the study were in addition to those achieved with the patients' existing therapeutic regimens.

There were no new areas of safety concerns identified in the trial. Of the 83 patients treated with mipomersen, 73 completed the study; nine of the discontinuations were related to adverse events. Consistent with previous studies evaluating mipomersen, the most commonly observed adverse events were injection site reactions and flu-like symptoms. As in other mipomersen trials, elevations in liver transaminases were observed that were similar in magnitude and duration to those seen in other studies. None of these patients had changes in other laboratory tests to indicate hepatic dysfunction, and there were no Hy's Law cases. Full data from this study will be presented at a future medical meeting.

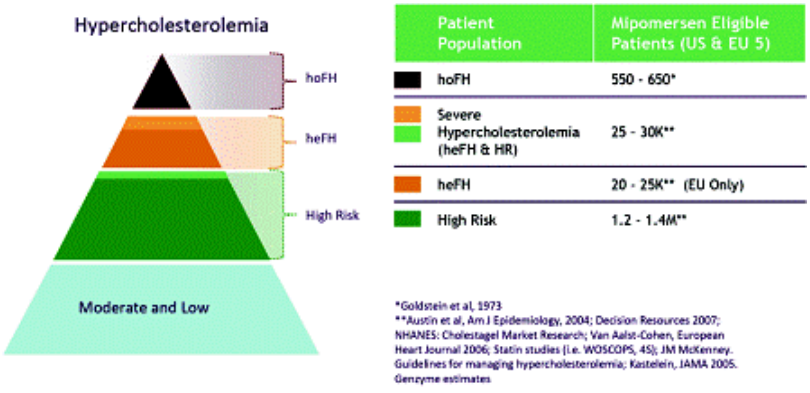
We and Genzyme are currently conducting a broad clinical program evaluating mipomersen in different patient populations. We have completed enrollment in the following mipomersen studies including:

- A Phase 3 study in 58 patients with severe high cholesterol;
- A Phase 3 study in 158 high cholesterol patients at high risk for coronary heart disease; and
- A Phase 2 study in high-risk, high-cholesterol patients who are intolerant to statins.

We and Genzyme expect to report the data from the remaining two Phase 3 studies in mid-2010. The data from all of the Phase 3 mipomersen clinical studies will help inform the design of a clinical outcomes study of mipomersen. The outcomes study may also support the eventual potential expansion of mipomersen's label to include a broader group of high-risk, high-cholesterol patients.

Mipomersen Commercialization — The U.S. Food and Drug Administration, or FDA, has granted mipomersen Orphan Drug designation for treating patients with homozygous FH. Orphan Drug designation encourages and facilitates development of drugs for rare diseases, offering potential tax credits and marketing incentives upon approval.

Genzyme's initial U.S. and E.U. regulatory filings for mipomersen will seek marketing approval for the treatment of patients with homozygous FH. These two filings may also include patients with severe hypercholesterolemia. A Phase 3 study of mipomersen in patients with severe hypercholesterolemia is fully enrolled and we anticipate data in mid-2010. With the completion of enrollment in this study, the last of the four Phase 3 studies that will form the basis for the first regulatory filings, Genzyme continues to refine and expand the regulatory and commercial strategy for mipomersen. By mid-2011, Genzyme expects to have filed for approval in the U.S. and E.U. and to have made progress toward filing in other major international markets. In addition, we and Genzyme expect that data from all of the mipomersen trials described above will be available at the time of the initial submissions, and this data will continue to build the body of clinical evidence around mipomersen's value in managing high-risk, high-cholesterol patients. Following a successful severe hypercholesterolemia submission in Europe, Genzyme plans to file a second submission in Europe for heterozygous FH patients. Genzyme and Isis are also planning an outcomes study that may support the potential expansion of mipomersen's indication to include a broader group of high-risk, high-cholesterol patients.



ISIS-CRP$_{Rx}$ — ISIS-CRP$_{Rx}$ is an antisense drug that targets CRP, a protein produced in the liver. CRP levels increase dramatically during inflammatory disorders, and excessive amounts of CRP have been linked to coronary artery disease. Furthermore, a growing body of evidence from clinical trials implicates CRP in cardiovascular disease progression.

These results suggest that it may be therapeutically beneficial to significantly decrease CRP levels in patients who are at risk for coronary events. In addition, clinicians have associated elevated CRP levels with a worsening of overall outcomes in conditions such as end-stage renal disease and multiple myeloma, suggesting that lowering CRP could help these patients. CRP elevation is also evident in many other major inflammatory diseases such as Crohn's disease and rheumatoid arthritis.

In preclinical studies, we observed dramatic suppression of liver and serum CRP levels with our antisense inhibitor of CRP. ISIS-CRP$_{Rx}$ is currently in a Phase 1 blinded, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of our drug in addition to the initial effects of our drug on baseline CRP levels in healthy volunteers. Once completed, we intend to initiate a broad Phase 2 program on ISIS-CRP$_{Rx}$ and evaluate ISIS-CRP$_{Rx}$ in patients with multiple myeloma, rheumatoid arthritis with stable high CRP levels, atrial fibrillation following cardiopulmonary bypass and end-stage renal disease.

BMS-PCSK9$_{Rx}$ — BMS-PCSK9$_{Rx}$ is an antisense drug that specifically targets proprotein convertase subtilisin/kexin type 9, or PCSK9, an important protein involved in the metabolism of cholesterol and LDL. Its role is to break down the cell surface receptor that captures LDL particles. Therefore, inhibiting PCSK9 increases the number of receptors available to remove LDL-C from the bloodstream. Genetic studies in humans have demonstrated that elevated PCSK9 can lead to severely high levels of LDL-C, whereas low PCSK9 is associated with low LDL-C levels. These observations suggest that it may be therapeutically beneficial to decrease PCSK9 levels in patients who are at risk for atherosclerosis and cardiovascular disease. We believe that BMS-PCSK9$_{Rx}$ could offer a new and complementary mechanism to current lipid-lowering therapies to prevent and treat cardiovascular diseases.

In May 2007, Bristol-Myers Squibb entered into a collaboration with us to identify antisense drugs that target PCSK9. In 2008, we achieved the first milestone in this collaboration with the selection of BMS-PCSK9$_{Rx}$ as a development candidate.

ISIS-FXI$_{Rx}$ — ISIS-FXI$_{Rx}$ is an antisense drug designed to treat clotting disorders. It targets Factor XI, a clotting factor produced in the liver. High levels of Factor XI are linked to heart attack, stroke and blood clots. In preclinical studies, ISIS-FXI$_{Rx}$ demonstrated potent antithrombotic activity and a superior safety profile (lower risk of bleeding) compared with standard anti-clotting agents, including low molecular weight heparin, warfarin and Factor Xa inhibitors. We plan to begin IND-enabling studies on ISIS-FXI$_{Rx}$ in the first half of 2010.

ISIS-APOCIII$_{Rx}$ — ISIS-APOCIII$_{Rx}$ is an antisense drug designed to lower triglycerides to treat hypertriglyceridemia. Hypertriglyceridemia is an independent risk factor for cardiovascular disease and is also a hallmark of metabolic syndrome, which occurs in a large percentage of people with type 2 diabetes. ISIS-APOCIII$_{Rx}$ targets apolipoprotein C-III, or apoC-III, a protein synthesized in the liver that plays a central role in the regulation of serum triglycerides. Recent data suggest that loss-of-function mutations within the apoC-III gene lower triglycerides levels and appear to improve health and extend longevity. Clinical studies have demonstrated an association between apoC-III, metabolic syndrome and coronary heart disease. In addition, insulin resistance has been shown to be mediated through apoC-III, leading to worsening of the metabolic syndrome.

In preclinical studies, ISIS-APOCIII$_{Rx}$ mitigated symptoms of metabolic syndrome and reduced atherosclerosis in mice. We added ISIS-APOCIII$_{Rx}$ to our development pipeline in late 2009.

Cardiovascular research — We continue to build our cardiovascular disease franchise by evaluating potential drug targets that influence the onset and progression of cardiovascular disease, and we intend to expand our franchise with additional drugs to treat various aspects of cardiovascular disease through complementary mechanisms. We recently added ISIS-APOCIII$_{Rx}$ to our pipeline for the treatment of hypertriglyceridemia. We designed ISIS-APOCIII$_{Rx}$ to manage triglycerides levels and provide an alternate, yet complementary, approach to lipid management.

Metabolic Franchise

We are pursuing the discovery and development of antisense drugs for metabolic diseases such as diabetes and obesity. These chronic diseases affect millions of people and there continues to be a significant need for new therapies for these patients. According to the Centers for Disease Control and Prevention, diabetes affects more than 20 million people in the U.S., or 7 percent of the population, with type 2 diabetes constituting 90 percent to 95 percent of those cases.

ISIS 113715 — ISIS 113715 is an antisense drug that targets PTP-1B for the treatment of type 2 diabetes. PTP-1B is responsible for turning off the activated insulin receptor. As a result, by reducing levels of PTP-1B, ISIS 113715 enhances the activity of insulin. We plan to initially develop ISIS 113715 as an adjunct to insulin therapy. ISIS 113715 provides us with the opportunity to develop a first-in-class drug with a novel mechanism of action and an insulin signal enhancer with anti-obesity and lipid-lowering potential.

Scientists have long recognized PTP-1B as an attractive target for treatment of 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. Our antisense technology allows us to design very specific drugs that inhibit PTP-1B and that do not inhibit other protein family members, making it possible to reduce PTP-1B activity without affecting other closely related proteins that would likely lead to unwanted side effects.

In October 2009, we reported positive top-line Phase 2 data for ISIS 113715 in patients with type 2 diabetes who had uncontrolled blood sugar despite treatment with stable doses of sulfonylurea. The study showed consistent and statistically significant reductions in multiple short and intermediate measures of glucose control. In addition to lowering blood glucose, ISIS 113715 caused statistically significant and clinically meaningful reductions in LDL cholesterol. Furthermore, consistent with the preclinical data with ISIS 113715, a tendency toward weight loss was observed even in this short-term study without strict dietary control. The effect of ISIS 113715 on weight was preceded by a statistically significant increase in circulating adiponectin, a hormone that increases with weight loss. ISIS 113715 demonstrated a favorable safety profile with no exacerbation of sulfonylurea-induced hypoglycemia or other clinically significant adverse effects. We plan to report the full details of the data at a future medical meeting.

ISIS-GCGR$_{Rx}$ — ISIS-GCGR$_{Rx}$ is an antisense drug that targets GCGR. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, should lower blood glucose and help control type 2 diabetes.

In preclinical studies, we observed improved glucose control and reduced levels of blood triglycerides without producing hypoglycemia following treatment with an antisense inhibitor of GCGR. While this is justification enough to pursue GCGR as a therapeutic target, the additional activity of our GCGR drug in increasing circulating glucagon-like peptide, or GLP-1, makes GCGR an even more attractive therapeutic target for development. GLP-1 is a hormone that helps to preserve pancreatic function, enhancing insulin secretion.

We recently reported Phase 1 data in which ISIS-GCGR$_{Rx}$ produced a significant improvement in glucagon-induced blood glucose levels and was well tolerated. In this study, normal volunteers were administered a glucagon infusion that caused an increase in blood glucose levels. Subjects treated with ISIS-GCGR$_{Rx}$ showed a dose-dependent decrease in blood glucose levels and at a dose of 400 mg/week of ISIS-GCGR$_{Rx}$ demonstrated statistically significant decreases in blood glucose following the glucagon infusion ($p<0.0001$).

ISIS-GCGR$_{Rx}$ was developed with Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, as part of a collaboration. During our research collaboration with OMJP, we identified more potent antisense inhibitors to GCGR. A more potent drug should enhance the therapeutic profile of the GCGR

program and provide much greater commercial value. This collaboration has ended and we have regained the rights to the glucagon receptor program. We will continue to pursue this target and plan to move a more potent inhibitor forward in development.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug that targets the glucocorticoid receptor, or GCCR. Glucocorticoid hormones have a variety of effects throughout the body, including promoting liver glucose production and fat storage. Although scientists have long recognized inhibiting GCCR as an attractive strategy for developing therapeutics for type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged developers of traditional drugs. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to antagonize glucocortocoid action primarily in liver and fat tissue. Notably, antisense drugs do not reduce GCCR expression in the central nervous system, or CNS, or adrenal glands, which could lead to systemic side effects.

In preclinical studies, we have shown that antisense inhibition of GCCR reduced levels of blood glucose, demonstrated a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and reduced body fat. These observations suggest that an antisense drug that inhibits GCCR could have a broad therapeutic profile. We were developing our GCCR program as part of our collaboration with OMJP. OMJP has returned the program to us, and we will be moving this program forward in development.

ISIS-SGLT2$_{Rx}$ — ISIS-SGLT2$_{Rx}$ is an antisense drug that targets sodium glucose co-transporter type 2, or SGLT2, which is the major transporter for blood sugar re-absorption in the kidney. By specifically blocking the production of SGLT2 in the kidney tissue, we can promote blood sugar excretion and reduce blood sugar levels, without having any effect on a related gene product, SGLT1.

In addition to being our first antisense drug directed at a target in the kidney, ISIS-SGLT2$_{Rx}$ is also unique due to its 12 nucleotide length rather than the more typical 18 to 21 nucleotide sequences that comprise our other drugs. It is among the most potent antisense drugs that we have evaluated in preclinical models. In preclinical studies, inhibition of SGLT2 was very potent in reducing blood glucose levels and hemoglobin, or HbA1c, which is a measure of long-term glucose control, without causing low blood sugar, called hypoglycemia. These data are consistent with expectations based on human subjects who have mutations in the SGLT2 gene and have increased urine glucose levels but are otherwise asymptomatic. Therefore, we believe that ISIS-SGLT2$_{Rx}$ could be a potent, highly active drug that will provide significant therapeutic benefits.

We are evaluating ISIS-SGLT2$_{Rx}$ in a Phase 1 study designed to assess the safety and activity of the drug in healthy volunteers by measuring the effect on glucose excretion in urine. We plan to complete the ongoing Phase 1 study of ISIS-SGLT2$_{Rx}$ and expect to initiate a Phase 2 study in 2010.

Cancer Franchise

We are pursuing the discovery and development of antisense drugs to treat cancers internally and through our partnerships with OncoGenex and Eli Lilly and Company. Cancer is one of our core therapeutic areas and an area where we are expanding our internal development activities. During 2009, our partners presented encouraging clinical data on a number of antisense drugs, including positive Phase 2 overall median survival data for OGX-011. We discovered or co-discovered these antisense drugs and licensed them to our partners to treat multiple types of cancer. We believe the favorable tolerability and early evidence of clinical benefit of these partnered drugs demonstrate how uniquely suited our technology is to create novel cancer therapeutics. Because of these observations, we have begun to build our internal cancer program, and, as a first step, we reacquired the rights to ISIS-EIF4E$_{Rx}$, an antisense drug we discovered and previously licensed to Eli Lilly and Company for the treatment of cancer. By reacquiring this important cancer program we can rapidly advance the program to Phase 2 studies in patients with multiple types of cancer. In addition to ISIS-EIF4E$_{Rx}$, our current portfolio consists of three antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. We believe that our antisense drugs have pharmaceutical properties that make them attractive therapeutics for cancer, and we continue to expand our efforts in cancer to include new targets and new treatments.

OGX-011 — OGX-011, now under license to Teva Pharmaceutical Industries Ltd., is a second-generation antisense drug that targets clusterin, a secreted protein that acts as a cell-survival protein and is over-expressed in response to anti-cancer agents. We and OncoGenex jointly discovered and conducted the initial development of OGX-011. OGX-011 is designed to be used as an adjunct therapy to enhance the effectiveness of chemotherapy and has shown promising results when added to currently available chemotherapies in several tumor types. The FDA has granted OGX-011 two Fast Track Designations as a treatment in combination with first-line and second-line docetaxel for progressive metastatic prostate cancer. In December 2009, OncoGenex licensed OGX-011 to Teva as part of a global license and collaboration agreement to develop and commercialize OGX-011.

In May 2009, OncoGenex reported results of a randomized Phase 2 trial of OGX-011 in patients with advanced metastatic castrate resistant prostate cancer, or CRPC, at the American Society of Clinical Oncology. In this study, OncoGenex reported a median overall survival of 23.8 months in patients treated with OGX-011 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 OGX-011. OncoGenex also reported that OGX-011 continued to be well tolerated in combination with docetaxel.

OncoGenex has also evaluated OGX-011 in a Phase 1/2 combination study in patients with non-small cell lung cancer, or NSCLC. In February 2009, OncoGenex reported data showing that after two years, 30 percent of patients who had received OGX-011 with first-line chemotherapy were still alive. Previously, OncoGenex reported a mature median survival of 14.1 months and a one-year survival rate of 54 percent.

Teva and OncoGenex will collaborate on a global Phase 3 clinical program in patients with advanced prostate cancer and advanced NSCLC. OncoGenex has announced that, together with Teva, it expects to initiate two Phase 3 clinical studies in 2010. These studies include a Phase 3 study for second-line chemotherapy in patients with CRPC and a Phase 3 study for first-line chemotherapy in patients with metastatic CRPC. OncoGenex also announced that, together with Teva, it intends to initiate an additional Phase 3 study in first-line treatment in patients with advanced, unresectable NSCLC by early 2011.

LY2181308 — LY2181308 is an antisense drug that targets survivin, which plays a role in cancer cell death and is one of the most commonly over expressed proteins in cancers. We licensed our anti-cancer drug, LY2181308, to Eli Lilly and Company as part of the companies' antisense drug discovery

research collaboration in cancer. The researchers involved in this collaboration have shown that inhibiting the expression of survivin by LY2181308 inhibits the growth of cancer cells. Since normal cells in the body do not express survivin, we expect that this drug will have fewer side effects than traditional chemotherapy. Eli Lilly and Company completed its Phase 1 study of LY2181308 and presented first-in-human data from this study confirming that LY2181308 penetrates tumor tissue and reduces survivin messenger RNA, or mRNA, and protein levels in tumor cells.

Eli Lilly and Company is evaluating LY2181308 in two separate Phase 2 studies in patients with relapsed or refractory acute myeloid leukemia and as a combination therapy in patients with hormone refractory prostate cancer. In addition, Eli Lilly and Company continues to progress in Phase 2 studies of LY2181308 in patients with a variety of cancers.

ISIS-EIF4E$_{Rx}$ — ISIS-EIF4E$_{Rx}$ is an antisense drug that targets eukaryotic initiation factor-4E, or eIF-4E, a protein involved in the translation of key growth and survival factors that contribute to tumor progression and the spread of cancer. eIF-4E is upregulated or overexpressed in a variety of cancers, including breast, head and neck, prostate, lung, bladder, colon, thyroid and non-Hodgkin's lymphomas and is involved in the translation of key growth and survival factors that contribute to tumor progression and the spread of cancer. Targeting eIF-4E has been of great interest to the pharmaceutical industry and the oncology community, however the pharmaceutical industry considers eIF-4E a difficult protein to target with traditional pharmaceutical approaches. In conjunction with scientists from Eli Lilly and Company and the Wood Hudson Cancer Research Laboratory, we published experimental data in The Journal of Clinical Investigation that suggests eIF-4E may act as a critical "switch" in cancer progression.

ISIS-EIF4E$_{Rx}$, formerly known as LY2275796, was discovered by us and licensed to Eli Lilly and Company for the treatment of cancer. In December 2009, we reacquired ISIS-EIF4E$_{Rx}$ from Eli Lilly and Company. With the reacquisition of this asset, we will independently develop ISIS-EIF4E$_{Rx}$ through Phase 2 proof-of-concept for the treatment of multiple types of cancer, potentially including, breast, lung, prostate, bladder and colon cancers. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development.

Eli Lilly and Company completed a Phase 1 study of ISIS-EIF4E$_{Rx}$ in patients with cancer that showed that the drug was well tolerated at doses up to 1200 mg per week. We plan to initiate a broad Phase 2 program on ISIS-EIF4E$_{Rx}$ in 2010.

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

OncoGenex is evaluating OGX-427 in patients with cancer. In May 2009, OncoGenex reported preliminary results from a Phase 1 study of OGX-427 in patients with a variety of cancers. In this study, treatment with OGX-427 was well tolerated as a monotherapy and demonstrated declines in circulating tumor cells at all doses evaluated as well as evidence of reduction in tumor markers defined as declines of prostate-specific antigen, or PSA, levels in prostate cancer and cancer-antigen-125 levels in ovarian cancer. In August 2009, OncoGenex announced the initiation of another Phase 1 study of OGX-427 in patients with bladder cancer.

In early 2010, OncoGenex announced that a randomized, controlled Phase 2 clinical study evaluating OGX-427 as a monotherapy in patients with CRPC has received grant funding. OncoGenex reported that it expects the Phase 2 study to start by mid-2010.

Neurodegenerative Franchise

We are pursuing the discovery and development of antisense drugs for neurodegenerative diseases in which there is a large unmet need for new treatment options. Our goal is to develop antisense drugs to treat diseases with identified genetic causes. We have initiated several programs to develop drugs to treat severe neurodegenerative disease and funded three of these programs through grants. In addition, as part of our alliance with Genzyme, we have a preferred partner relationship for the development and commercialization of antisense drugs for certain neurodegenerative and rare diseases. Our most advanced neurodegenerative program is ISIS-SOD1$_{Rx}$, an antisense drug to treat amyotrophic lateral sclerosis, or ALS, also known as Lou Gehrig's disease. In December 2009, we announced the advancement of another drug, ISIS-SMN$_{Rx}$ for the treatment of SMA to our pipeline. ISIS-SMN$_{Rx}$ is the first antisense drug to enter our pipeline that modulates splicing, an alternate antisense mechanism.

ISIS-SOD1$_{Rx}$ — ISIS-SOD1$_{Rx}$ is an antisense drug that targets superoxide dismutase, or SOD1, a molecule associated with an inherited, aggressive form of ALS. The FDA granted ISIS-SOD1$_{Rx}$ Orphan Drug designation for the treatment of ALS. Because antisense drugs do not cross the blood-brain barrier, a small pump administers the drug directly into the CNS infusing the drug into the cerebral spinal fluid. Clinicians call this type of administration intrathecal infusion.

Researchers reported in the Journal of Clinical Investigation that treatment with ISIS-SOD1$_{Rx}$ prolonged life in rats that showed many symptoms of ALS. By delivering our drug directly to the fluid that circulates within the CNS, we and our collaborators lowered production of the mutant protein in neurons and surrounding cells.

The ALS Association and the Muscular Dystrophy Association are providing funding for ISIS-SOD1$_{Rx}$. Additionally, as part of our alliance with Genzyme, Genzyme has a right of first negotiation to license ISIS-SOD1$_{Rx}$ from us. We plan to initiate a Phase 1 study of ISIS-SOD1$_{Rx}$ in patients with the familial form of ALS in 2010.

ISIS-SMN$_{Rx}$ — ISIS-SMN$_{Rx}$ is an antisense drug designed to treat SMA, a neuromuscular disorder and the leading genetic cause of infant mortality. The incidence of SMA is 1 in 6,000 to 10,000 births, and most infants born with the most severe form of SMA, Type 1, die within two years according to the National Institutes of Health's National Institute of Neurological Disorders and Stroke. A genetic deletion of the survival motor neuron 1, or SMN1, gene is responsible for SMA. ISIS-SMN$_{Rx}$ increases the production of the protein SMN by modulating the splicing of a closely related pre-mRNA, SMN2. Normal motor function is associated with normal levels of SMN. By altering splicing to produce SMN, ISIS-SMN$_{Rx}$ may compensate for the underlying genetic defect.

In 2008, we and researchers from Cold Spring Harbor published data that demonstrated the feasibility of using our antisense technology to control splicing. Our collaborative work with Cold Spring Harbor led to the discovery of ISIS-SMN$_{Rx}$. Our SMA program is part of our collaboration in

neurodegenerative disease with Genzyme, pursuant to which Genzyme has a right of first negotiation to license ISIS-SMN_{Rx} from us. We plan to initiate IND-enabling studies on ISIS-SMN_{Rx} in 2010.

Other Drugs in Development

The broad applicability of our antisense technology allows us to create promising drugs in a variety of disease areas, many of which are underserved with current treatment options. For instance, our partner, Altair, recently presented encouraging Phase 1 data from our first inhaled antisense drug, AIR645, in patients with mild asthma. AIR645 is now being evaluated in a Phase 2a study and, if effective, it could offer a new non-steroidal, anti-inflammatory treatment for patients with asthma. AIR645 is our first inhaled antisense drug to enter human studies and is an example of the different routes of administration to optimize distribution that we can utilize. We have been successful in developing novel drugs and licensing them to highly focused satellite companies that have the specific expertise and resources to continue developing these drugs. Together with our partners we continue to advance drugs in clinical development that are outside of our core therapeutic areas.

ACHN-490 — ACHN-490 is a next-generation aminoglycoside, or neoglycoside, drug that Achaogen 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. ACHN-490 incorporates aminoglycoside technology that we licensed to Achaogen. In earlier studies, ACHN-490 displayed broad-spectrum activity against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli and methicillin-resistant staphylococcus aureus, or MRSA. In preclinical studies, ACHN-490 demonstrated an acceptable safety profile and the potential for once-daily dosing. In September 2009, Achaogen reported the successful completion of a Phase 1 study on ACHN-490. Achaogen plans to initiate a Phase 2 study on ACHN-490 in 2010.

AIR645 — AIR645 is an inhaled second generation antisense drug that targets the alpha subunit of the interleukin 4 receptor, or IL-4R-alpha, which inhibits interleukin 4, or IL-4, and interleukin 13, or IL-13, signaling. IL-4 and IL-13 are two important cytokines in asthma, which regulate inflammation, mucus overproduction and airway hyper-responsiveness. In 2007 we licensed AIR645 to Altair, a company focused on the discovery, development and commercialization of novel therapeutics to treat human respiratory diseases. In preclinical studies, we showed that inhibiting IL-4R-alpha with an antisense compound potently reduced target RNA and protein levels. Inhibiting IL-4R also demonstrated pharmacologic activity in mouse models of asthma that included reducing lung cytokine production, inflammation, and airway hyper-responsiveness. In addition, these studies showed that, when delivered by inhalation, AIR645 rapidly distributed to the airways and achieved therapeutic drug concentrations in multiple cell types with little systemic exposure.

In September 2009, Altair reported the successful completion of a Phase 1 study on AIR645 evaluating the safety and tolerability of AIR645 in healthy volunteers. Researchers presented the Phase 1 results at the European Respiratory Society Annual Congress that showed treatment with AIR645 was safe and well tolerated in subjects. In November 2009, Altair initiated a Phase 2 study of AIR645 in patients with mild asthma. Altair expects to report results from this trial in the third quarter of 2010.

Alicaforsen — Now under license to Atlantic Pharmaceuticals Limited, alicaforsen is an antisense drug that targets intercellular adhesion molecule 1, or ICAM-1. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, including ulcerative colitis and pouchitis. Ulcerative colitis is an inflammatory bowel disease of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in ulcerative colitis patients who have had their diseased colons removed. In 2007, we licensed alicaforsen to Atlantic Pharmaceuticals for pouchitis, ulcerative colitis and other inflammatory diseases. The FDA and European Medicines Agency have since granted alicaforsen Orphan Drug Designation for the treatment of pouchitis in the US and Europe respectively. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

ATL/TV1102 — Now under license to Teva, ATL/TV1102 is an antisense inhibitor of CD49d, which is 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 ATL/TV1102 to Antisense Therapeutics Limited in December 2001 and, in February 2008, ATL licensed ATL/TV1102 to Teva, which has responsibility for continued development of ATL/TV1102. In 2008, Teva and ATL reported Phase 2a results of ATL/TV1102 showing significantly reduced disease activity in patients with relapsing remitting MS, for which we earned a milestone payment. Teva is completing additional preclinical studies prior to continuing to longer-term dosing studies in patients with MS.

ATL1103 — ATL1103 is an antisense drug that targets 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, which is characterized by abnormal growth of organs, face, hands and feet, as well as for diabetic retinopathy, a common disease of the eye and a leading cause of blindness. In preclinical studies, ATL1103 demonstrated significant reductions in IGF-1 levels in the blood. ATL has recently completed preclinical toxicity studies on ATL1103 and expects to submit an application to conduct a human clinical trial in the second half of 2010.

EXC 001 — EXC 001 is an antisense drug we co-discovered and licensed to Excaliard for the local treatment of fibrotic diseases, including scarring. Fibrosis represents a significant and expanding area of unmet medical need where antisense drugs could offer a unique advantage for anti-fibrotic agents. Excaliard reported the successful completion of a Phase 1 study on EXC 001 and has initiated three Phase 2 studies on EXC 001.

iCo-007 — iCo-007 is an antisense drug that targets c-Raf kinase. In preclinical studies, antisense inhibition of c-Raf kinase was associated with a reduction in the formation and leakage of new blood vessels in the eye, suggesting inhibiting c-Raf kinase can improve treatment for both diabetic macular edema and diabetic retinopathy. Diabetic retinopathy is one of the leading causes of blindness in people in the U.S., and nearly 100 percent of type 1 diabetics by age 20 have evidence of retinopathy. Additionally up to 21 percent of people with type 2 diabetes have retinopathy when they are first diagnosed with diabetes, and most will eventually develop some degree of retinopathy. We discovered iCo-007 and licensed it to iCo for the treatment of various eye diseases that occur as complications of diabetes.

In early 2009, investigators evaluating iCo-007 in patients with diffuse Diabetic Macular Edema presented results from the first two cohorts of a Phase 1 study. In August 2009, iCo completed enrollment of the fourth and last cohort. iCo expects to present the final data from the Phase 1 study in the second quarter of 2010.

Vitravene, or fomivirsen — In August 1998, the FDA approved Vitravene, an antisense drug that we discovered and developed, to treat cytomegalovirus, or CMV retinitis in AIDS patients. Novartis Ophthalmics AG, our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis no longer markets Vitravene. Vitravene demonstrates our ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs.

Antisense Technology

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. We can design our antisense drugs to target a broad range of diseases, efficiently producing a proprietary portfolio of drugs that can interrupt the production of disease-causing proteins without disrupting other proteins that are necessary for the body's normal functions. We are currently pursuing antisense drug discovery programs focused on various cardiovascular, metabolic, neurodegenerative, and other diseases as well as 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. This highly specific nucleotide pairing is called 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 so doing, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the synthesis of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the "sense" strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Specifically, almost all of our antisense drugs in development cause a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target mRNA. The drug itself remains intact during this process, so it can remain active against additional target mRNA molecules and repeatly trigger their degradation. Our antisense drugs can selectively bind to a 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 design directed at protein targets. Traditional drug design requires companies to identify a small molecule that will interact with protein structures to affect the disease-causing process. Since predicting which small molecules will do this has proven to be difficult, traditional drug discovery involves testing hundreds of thousands of small molecules for their ability to interfere with protein function. As a result, traditional drug discovery is a labor intensive, low probability endeavor. In contrast, we design our antisense compounds to bind to mRNA through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the target mRNA.

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. Furthermore, because of the nature of antisense drugs, the very molecules we design for gene functionalization and target validation experiments may become our lead drug candidates. This efficiency is a unique advantage of our antisense drug discovery. 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. We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drugs. The goal of our target-based research programs is to identify antisense drugs to treat diseases for which there are substantial markets and for which there is a need for better drugs. In addition, our research programs focus on developing the next-generation technology that we expect will increase the potency of our drugs and that could make oral bioavailability viable. We expect that these next-generation drugs will serve as follow-on compounds to our current drugs in development and to our development candidates.

Other Antisense Mechanisms

RNAi

In addition to advancing our RNase H1 mediated antisense drugs and core chemistries, we are also working to understand the potential therapeutic utility of more nascent antisense mechanisms, including RNA interference, or RNAi, and regulation of alternative splicing. For some of this research we work with satellite company partners, including Alnylam.

RNAi is an antisense mechanism that involves using small interfering RNA, or siRNA, as a method to target a mRNA sequence. With siRNA, the cell utilizes a protein complex called RNA-induced silencing complex, or RISC, to bind to the mRNA and to prevent the production of a disease-causing protein. We have a strong and growing intellectual property position in RNAi methodology and oligonucleotide chemistry for siRNA therapeutics, and we have licensed these patents to Alnylam for double-stranded siRNA therapeutics and some single-stranded siRNAi therapeutics, as part of our collaboration with them.

At present, the double-stranded siRNA drugs in development are administered locally, or, to achieve sufficient systemic delivery, require special chemical formulation of the oligonucleotides. In contrast, our single-stranded second generation antisense drugs readily distribute to target organs including liver and kidney. As part of our overall research efforts, we have discovered strategies for designing single-stranded olionucleotides that act through the RNAi mechanism. With further development, these chemically modified, single-stranded, RNA-like oligonucleotides could have improved properties for systemic administration while harnessing certain advantages of the RNAi mechanism.

In April 2009, we announced that we have formed a new collaboration with Alnylam that will focus on the development of single-stranded RNAi technology. As part of the collaboration, we co-exclusively licensed our single-stranded RNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments and royalties. The alliance provides Alnylam with access to our intellectual property and expertise regarding the development of single-stranded RNAi antisense drugs, while both we and Alnylam will have the opportunity to discover and develop drugs employing the new technology.

Splicing

Splicing is a normal cellular mechanism that the cell uses in order to produce many different, but closely related proteins from a single gene by varying the processing of the RNA. It is estimated that of the approximately 25,000 genes in the human genome, 40 percent to 60 percent have alternative splice forms. In some cases, alternative splicing of proteins results in the production of proteins involved in disease. In other cases, alternative splicing can result in the omission of proteins that are critical for normal cellular function which can lead to disease. Using antisense technology, we can direct alternate splicing to produce a protein critical for normal cellular function and potentially correct for a genetic defect. Examples of applications of antisense modulation of splicing to treat genetic disease include, SMA, thalessemia, cystic fibrosis and Duchenne's muscular dystrophy.

In December 2009, we advanced into development the first antisense drug, ISIS-SMN$_{Rx}$, that modulates splicing. We designed ISIS-SMN$_{Rx}$ to treat the splicing disease, SMA, which is a neuromuscular disorder and the leading genetic cause of infant mortality. The discovery of ISIS-SMN$_{Rx}$ resulted from a joint research collaboration between scientists at Isis and Cold Spring Harbor. In earlier published research, we and our collaborators at Cold Spring Harbor demonstrated the feasibility of using our antisense technology to control splicing for the treatment of SMA.

Our progress in controlling splicing to treat disease demonstrates the diversity of our technology and the potential to utilize many different antisense approaches to treat disease.

New Antisense Targets

MicroRNAs

There are many different types of RNA that exist within the body, including pre-mRNAs and mRNAs. Our antisense technology is not limited to RNA sequences that translate into proteins, but rather we can apply the principals of our technology to develop drugs that target other RNAs, such as microRNAs. MicroRNAs are small, non-coding RNA

molecules, typically 20 to 25 nucleotides in length, 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. 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 are associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. MicroRNAs themselves may be drug targets. For instance, if a single microRNA can change the expression of a protein that may be involved in disease, then inhibiting this microRNA could provide a therapeutic benefit. Alternately, microRNAs could be used as drugs themselves, where increasing the cell concentration of a particular microRNA could modulate the expression of a particular protein. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-based therapeutics.

Other Oligonucleotide Opportunities

Scientists can also design oligonucleotide molecules to directly target and bind to proteins to treat diseases. Aptamers are oligonucleotide molecules that form a three-dimensional shape that specifically bind to a protein molecule of interest for disease treatment. Aptamers differ from antisense inhibitors because they do not bind to an RNA sequence to inhibit protein formation, but rather they modify the function of a protein by binding directly to the protein. However, our patented chemical toolbox can greatly improve the chance that an aptamer will succeed as a drug. For example, we entered into a collaboration with Archemix to leverage aspects of our oligonucleotide chemistries, including manufacturing, for the development of aptamer drugs. As part of the agreement, Archemix gained access to part of our significant intellectual property estate relating to oligonucleotide chemical modifications in exchange for equity, milestone payments and royalties on aptamer drugs Archemix develops.

Regulus Therapeutics

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics. In addition, Regulus has assembled a strong leadership team with corporate management, business and scientific expertise, a board of directors that includes industry leaders in drug discovery and development, and a scientific advisory board that consists of world-class scientists including some of the foremost authorities in the field of microRNA research.

Regulus Business

We and Alnylam granted Regulus exclusive licenses to our intellectual property for microRNA therapeutic applications, and Alnylam made an initial investment in Regulus of $10 million in 2007 to balance venture ownership. In early 2009, Regulus raised a $20 million in a Series A preferred stock financing in which we and Alnylam were sole and equal investors in the financing. We own 51 percent of Regulus and Alnylam owns the remaining 49 percent. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

We and Alnylam provide Regulus with research and development and general and administrative services under the terms of a services agreement and in accordance with an operating plan mutually agreed upon by us and Alnylam.

Regulus exclusively controls many of the early fundamental patent portfolios in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Our "Crooke" patent estate provides Regulus exclusive rights to RNA-based product compositions and methods of treatment in the field of microRNA-based therapeutics. The Regulus patent estate also includes claims to specific microRNA compositions that are optimized for therapeutic use and exclusive rights to Isis' and Alnylam's chemical modification intellectual property estates for microRNA applications. In total, Regulus' intellectual property portfolio includes early fundamental intellectual property in the field of microRNA, as well as over 900 filed patent applications pertaining to chemical modification of oligonucleotides for therapeutic applications, of which over 600 patents have been issued.

In April 2008, Regulus formed a strategic alliance with GSK to discover, develop and market microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The transaction included a $20 million upfront payment to Regulus and up to $144.5 million in potential development, regulatory and sales milestone payments by GSK for each of the four microRNA-targeted therapeutics discovered as part of the collaboration. Additionally, Regulus is eligible to receive royalties up to double digits on worldwide sales of products resulting from the collaboration. In May 2009, Regulus achieved the first milestone in this collaboration.

In February 2010, Regulus announced the establishment of a new collaboration with GSK to develop and commercialize microRNA therapeutics targeting miR-122 for the treatment of hepatitis C virus infection, or HCV. Under the terms of the new collaboration, Regulus will receive additional upfront and early stage milestone payments with the potential to earn more than $150 million in miR-122-related combined payments. Under the terms of the HCV collaboration, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestones payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

Beginning in the first quarter of 2010, as a result of a new accounting standard, we will no longer include Regulus' revenue and operating expenses in our operating results and will no longer include Regulus' cash in our cash balance, which at December 31, 2009 was $30.7 million. See Note 1, *Organization and Significant Accounting Policies*, for a more detailed explanation of this change.

Regulus Therapeutic Programs

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, 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 diagnostic tool for disease characterization.

Regulus benefits from ours and Alnylam's microRNA research programs, which the companies combined to form Regulus. As a result, Regulus began with extensive expertise in microRNA biology, chemistry and informatics that supported the initiation of a comprehensive research and development program in several therapeutic areas, including oncology, immunology, inflammation and metabolic disease. Furthermore, Regulus is involved in a substantial number of academic collaborations that are increasing the understanding and evaluating the biology of over 60 different microRNAs.

Regulus has a lead program for HCV, focused on targeting the microRNA, miR-122, which is now part of Regulus' alliance with GSK. Regulus and scientists demonstrated that an oligonucleotide-based molecule targeting miR-122, anti-miR-122, reduced cholesterol levels in blood and reversed hepatic steatosis, or fatty liver, in obese mice. Researchers also reported that miR-122 is essential for replication of HCV, suggesting that an anti-miR-122 drug may reduce HCV infection and improve HCV-associated pathologies like fatty liver. Regulus is advancing anti-miR-122 toward clinical studies for HCV.

Regulus is also advancing a program for fibrotic diseases targeting miR-21. Regulus and collaborators demonstrated that anti-miR-21 can reverse fibrosis and significantly improve cardiac function in mice with failing hearts. Regulus' research and development efforts are also focused on other therapeutic areas including cardiovascular, oncology, immune-inflammatory, and metabolic disease. As part of Regulus' alliance with GSK, Regulus has a research program in inflammation, where GSK has an exclusive option to license drugs developed from the program.

Ibis Biosciences, Inc.

In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total acquisition price of $215 million. The Ibis technology is a product of our innovation and a tangible example of the value our technology provides outside of drug discovery and development. We are also eligible to receive an earn out on future sales of Ibis systems that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5 percent of net sales over $140 million through net sales of $2.1 billion and 3 percent of net sales over $2.1 billion, with the percentages subject to reduction in specified circumstances.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a clinical development pipeline of 22 drugs, to create a broad base of potential license fees, milestone payments, royalties, profit sharing and earn out payments and to control our drug development expenses. In this way, we remain a focused and efficient research and development organization that can continue to discover new drugs and expand ours and our partners' pipelines. In order to maximize the value of our antisense technology and our drug discovery platform, we pursue several different categories of partnerships, including traditional

pharmaceutical alliances and licenses, drug discovery and development satellite companies and technology development satellite companies. Our partnership strategy allows us to minimize our risk in discovering antisense drugs in new and underserved disease areas.

We concentrate on developing antisense drugs in our core therapeutic areas of cardiovascular, metabolic and neurodegenerative diseases and cancer. These are disease areas in which there are large market opportunities and we can quickly obtain clinical proof of concept. We generally license drugs from our core therapeutic franchises to traditional pharmaceutical partners after Phase 2 proof-of-concept and prior to the start of large Phase 3 programs.

Through the efficiency of our drug discovery platform we can develop drugs to almost any gene target. However, we focus on disease areas that are uniquely suited for antisense drugs. We license our drugs to pharmaceutical companies and to focused drug discovery and development satellite companies that dedicate themselves to advancing our drugs. Through this strategy we can expand the therapeutic range of antisense drugs into disease areas that need new and innovative treatment options.

Outside of our product pipeline, we also continue to enhance our core technology and intellectual property portfolios ensuring that we maintain technology leadership in RNA-based therapeutics. By leveraging our dominant intellectual property estate and our own investments in our core antisense technology, we benefit from our partners' successes in other RNA-based therapeutics.

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

Traditional Pharmaceutical Alliances and Licensing

We license our drugs to pharmaceutical partners for further development and commercialization and these partnerships benefit us, our drugs, and our partners. With the resources and experience of our pharmaceutical partners guiding drug development, our drugs should advance more rapidly and access larger markets than if we developed them on our own. Our partnering activity coupled with our efficient drug discovery technology enables us to develop the majority of our drugs that are in our core therapeutic areas through early proof-of-concept ourselves prior to licensing.

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a research relationship. The transaction, which closed in June 2008, 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 at $30 per share, over $1.5 billion in potential milestone payments and a share of profits on mipomersen and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. Under this alliance, Genzyme is responsible for the commercialization of mipomersen. We will contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter, we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme is our preferred partner for the development and commercialization of antisense drugs for certain neurodegenerative and rare diseases.

Genzyme has agreed that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen License and Co-Development Agreement, the first commercial sale of mipomersen or the termination of our mipomersen License and Co-Development Agreement. Thereafter, Genzyme will be

subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen License and Co-Development Agreement or the date Genzyme holds less than 2 percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

During 2009 and 2008, we recognized revenue of $66.4 million and $48.2 million, respectively, related to the upfront payments we received from Genzyme, which represented 55 percent and 45 percent, respectively, of our total revenue for those years.

Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with OMJP to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs. The collaboration ended and we regained the rights to drugs from both the glucagon receptor and glucocorticoid receptor programs. We intend to move a more potent inhibitor for our GCGR program forward that was identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program.

During 2009, 2008 and 2007, we recognized revenue of $18.4 million, $31.9 million and $13.2 million, respectively, related to the upfront licensing fee, the milestone payment and the research and development funding under this collaboration, which represented 15 percent, 30 percent and 23 percent, respectively, of our total revenue for those years.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting PCSK9. Under the terms of the agreement, we received a $15 million upfront licensing fee and Bristol-Myers Squibb agreed to provide us with at least $9 million in research funding over an initial period of three years. In April 2008, Bristol-Myers Squibb designated the first development candidate, BMS-PCSK9$_{Rx}$, resulting from the collaboration for which we earned a $2 million milestone payment. Under the agreement, we will also receive up to $166 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestone payments associated with development of follow-on compounds. Bristol-Myers Squibb will also pay us royalties on sales of products resulting from the collaboration. During 2009, 2008 and 2007, we recognized revenue of $9.1 million, $12.0 million and $5.2 million, respectively, related to the upfront licensing fee, milestone payment and the research funding, which represented 8 percent, 11 percent and 9 percent, respectively, of our total revenue for those years.

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Eli Lilly and Company, which included a joint antisense research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. Eli Lilly and Company is responsible for the preclinical and clinical development of LY2181308. As of December 31, 2009, we had earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308. We will receive additional milestone payments aggregating up to $25 million if LY2181308 achieves specified regulatory and commercial milestones, and in addition, royalties on future product sales of this drug.

In December 2009, we reacquired LY2275796, renamed ISIS-EIF4E$_{Rx}$, and will continue developing the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development.

During 2009, we earned revenue from our relationship with Eli Lilly and Company totaling $75,000, compared to $156,000 and $402,000 in 2008 and 2007, respectively.

Drug Discovery and Development Satellite Company Collaborations

Through our drug discovery and development satellite company collaborations, we continue to expand the reach and potential of RNA-based therapeutics into disease areas that are outside of our core focus areas. In addition, by capitalizing on our partners' resources and expertise, these partnerships allow more of our drugs to move forward in development than we could advance on our own. Further, 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. We refer to these companies as our drug discovery and development satellite companies, and this strategy as our satellite company strategy. With our satellite company strategy we can create and support a much broader product pipeline than we could develop on our own.

Achaogen, Inc.

In January 2006, we licensed our proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. In exchange for the exclusive, worldwide license to our aminoglycoside program, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. In January 2009, we received a $1 million milestone payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, as a result of the filing of an investigational new drug, or IND, for Achaogen's aminoglycoside drug, ACHN-490. At December 31, 2009 and 2008, we owned less than 10 percent of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $33.5 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products. During 2007 and 2008, we did not recognize any revenue from our relationship with Achaogen, compared to $500,000 revenue recognized in 2009, which does not include any revenue from the equity we received from Achaogen.

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a biotechnology company focusing on the discovery, development and commercialization of novel therapeutics to treat human respiratory diseases. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an antisense drug for the treatment of asthma. In November 2009, we participated in Altair's most recent financing, which will fund Altair's Phase 2 development of AIR645. As a result of the financing, our ownership interest in Altair was less than 10 percent at December 31, 2009, compared to approximately 18 percent at December 31, 2008. In addition to the preferred stock, we will receive additional license fees and royalties from Altair if AIR645 and other drugs arising out of the research collaboration progress. During 2009, 2008 and 2007, we recognized revenue of $79,000, $207,000 and $494,000, respectively, from our relationship with Altair, which does not include any revenue from the equity we received from Altair.

Antisense Therapeutics Limited

In December 2001, we licensed ATL/TV1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL/TV1102 to Teva. As part of our licensing agreement with ATL, we will receive one third of sublicense fees and milestone payments ATL receives from Teva as well as a percentage of any royalties. ATL and Teva reported encouraging data from a Phase 2a study on ATL/TV1102 in patients with relapsing and remitting MS. As a result of our licensing agreement and a milestone payment related to the data that ATL and Teva reported and Teva's decision to continue the development of ATL/TV1102, we earned $1.4 million, which we included in revenue in 2008. In 2009, we earned $2.0 million from Teva for manufacturing ATL/TV1102 drug product.

In addition to ATL/TV1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. ATL pays us cash for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009 we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership.

At December 31, 2009, our ownership percentage in ATL was approximately 10 percent of ATL's equity, compared to less than 10 percent at December 31, 2008. During 2009, we recorded revenue of $401,000 related to this collaboration compared to $1.6 million and $80,000 for 2008 and 2007, respectively.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based company that gastrointestinal drug developers founded in 2006 to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Pharmaceuticals plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed

by ulcerative colitis 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. At December 31, 2009 and 2008, we owned approximately 13 percent of Atlantic Pharmaceuticals' equity. In addition, assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen. During 2009, 2008 and 2007, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals. Because realization of the upfront equity payment is uncertain, we recorded a full valuation allowance.

Excaliard Pharmaceuticals, 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 have 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 a particular gene target. At December 31, 2009 and 2008, we owned less than 10 percent of Excaliard's equity and we have no remaining performance obligations. In early 2010, we participated in a financing and our ownership in Excaliard remains less than 10 percent. In addition, assuming Excaliard successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $8.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs Excaliard develops, as well as a portion of the fees Excaliard receives if it licenses the drugs. During 2009, 2008 and 2007, we recognized revenue of $290,000, $384,000 and $1 million, respectively, which does not include any revenue from the equity we received from Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007, a second-generation antisense drug. iCo is initially developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy. iCo paid us a $500,000 upfront fee and will pay us milestone payments totaling up to $22 million for the achievement of clinical and regulatory milestones. In addition, we will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In December 2006, iCo filed an IND application with the FDA for iCo-007 for which we earned a $200,000 milestone payment. In September 2007, iCo initiated Phase 1 clinical trials for iCo-007 and we earned a milestone payment of $1.25 million in the form of 936,875 shares of iCo's common stock.

Over the course of our relationship with iCo they have paid us in a combination of cash and equity instruments, which included common stock and convertible notes. In February 2009, iCo completed a CAD $1.3 million financing to fund the completion of its Phase 1 clinical study of iCo-007. We participated in the financing and as a result our ownership in iCo at December 31, 2009 was approximately 10 percent, compared to less than 10 percent at December 31, 2008. Subsequent to the end of the year, we exercised the warrants we held to purchase 1.1 million shares of iCo's common stock and as a result our ownership in iCo at January 31, 2010 was approximately 12 percent. During 2009, we recognized revenue of $14,000 from our relationship with iCo, compared to $7,000 for 2008. During 2007, we did not recognize any revenue from our relationship with iCo.

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement with OncoGenex. In December 2009, OncoGenex licensed OGX-011 to Teva for the treatment of multiple cancer indications. As part of our amended and restated agreement with OncoGenex, 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 milestone payments OncoGenex may receive from Teva in addition to up to 7 percent royalties on sales of OGX-011.

In August 2003, we and OncoGenex entered into a collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2009, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex will pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of the drug. As of December 31, 2009, OncoGenex had not triggered any of the milestone payments related to OGX-427.

In August 2008, OncoGenex completed a reverse takeover of Sonus Pharmaceuticals, a publicly traded company, and became a subsidiary of Sonus, which was renamed OncoGenex Pharmaceuticals, Inc. As a result of this transaction, our shares of OncoGenex preferred stock converted into 122,485 shares of OncoGenex common stock. During 2009, we sold all of the common stock of OncoGenex that we owned resulting in net cash proceeds of $2.8 million. As of December 31, 2009, we no longer owned any shares of OncoGenex. During 2009, we recognized revenue of $11.4 million from OncoGenex, compared to $4,000 in 2007. During 2008, we did not recognize any revenue from our relationship with OncoGenex.

Technology Development Satellite Company Collaborations

In addition to our traditional pharmaceutical alliances and drug discovery and development satellite company partnerships, we also have satellite company partnerships focused on developing and advancing certain RNA-based therapeutic technologies. These partnerships take advantage of our dominant

intellectual property estate, and leverage our own 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-based therapeutics and augment our active programs in these areas.

Archemix Corp.

In August 2007, we and Archemix entered into a strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to our technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than targeting mRNA. Through this licensing partnership, we are providing access to our oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs based on Archemix's technology. In November 2007, we received a $250,000 milestone payment from Archemix associated with the initiation of Phase 2a trials of their aptamer drug. In May 2009, we received a milestone payment from Archemix related to the advancement of their aptamer drug that incorporates our technology. We will receive a portion of any sublicensing fees Archemix generates as well as milestone payments and royalties on Archemix' drugs that use our technology. During 2009, we recognized $100,000 in revenue from Archemix, compared to $250,000 in 2007. During 2008, we did not recognize any revenue from our relationship with Archemix.

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 for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, the potential milestone payments from Alnylam total $3.4 million, which Alnylam will pay to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of double-stranded RNAi therapeutic targets and, except for the limited license we granted Alnylam in April 2009 described below, all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam at the time of the agreement.

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 RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of December 31, 2009, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of single-stranded RNAi, or ssRNAi, technology. As part of the collaboration, we have co-exclusively licensed our ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to our intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, we and Alnylam also extended our broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million, which we are amortizing over the three year period of our performance obligation based on the research plan included in the agreement. Alnylam will also pay us up to $20 million in additional license fees, which Alnylam will pay in three tranches that include $10 million in 18 months or earlier if *in vivo* efficacy in rodents is demonstrated sooner, $5 million upon achievement of *in vivo* efficacy in non-human primates, and $5 million upon initiation of the first clinical trial with an ssRNAi drug. Alnylam is funding research activities at a minimum of $3 million each year for three years with research and development activities conducted both at Isis and Alnylam. If Alnylam develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, we could potentially receive milestone payments, totaling up to $18.5 million per product, together with royalty payments. Also, initially we are eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam's partnering of ssRNAi products, which will decline over time as Alnylam's investment in the technology and drugs increases. In turn, Alnylam is eligible to receive up to 5 percent of any sublicense payments due to us based on our partnering of ssRNAi products. Both we and Alnylam are eligible to receive royalties from each other on any ssRNAi products developed by the other company. Alnylam has the right to terminate the ssRNAi research program before September 30, 2010, in which event any licenses to ssRNAi products granted by us to Alnylam under the agreement, and any obligation by Alnylam to pay milestone payments, royalties or sublicense payments to us for ssRNAi products under the agreement, would also terminate.

As of December 31, 2009, we had earned a total of $48.1 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics that Alnylam has granted to pharmaceutical partners.

During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2009, we no longer own any shares of Alnylam. During 2009, 2008 and 2007, we generated revenue from our relationship with Alnylam totaling $5.0 million, $4.6 million and $26.5 million, respectively, representing 4 percent, 4 percent and 45 percent, respectively, of our total revenue for those years.

Ercole Biotech, Inc.

In May 2003, we and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Part of this collaboration included a cross-license of our respective splicing-related intellectual property with Ercole. Under the collaboration, we combined our alternative splicing expertise with Ercole's to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, we granted Ercole a license to our Bcl-x molecule and some of our chemistry patents. Assuming Ercole successfully develops and commercializes a drug incorporating the splicing technology or chemistry we licensed to Ercole, we will receive milestone payments totaling up to $21 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of these drugs. Ercole is solely responsible for the continued development of its drugs.

Similarly, if we successfully develop and commercialize a drug incorporating the splicing technology Ercole licensed to us, we will pay milestone payments to Ercole totaling up to $21 million for the achievement of key clinical, regulatory and sales milestones and will also pay royalties to Ercole on

sales of these drugs. We currently do not have a drug incorporating Ercole's technology in clinical development.

In March 2008, AVI BioPharma, Inc. acquired Ercole's rights and obligations under the collaboration agreement. As a result of our collaboration agreement with Ercole, as part of the acquisition, we received a warrant to purchase 238,228 shares of AVI's common stock at an exercise price of $0.1679 per share, and a warrant to purchase 207,757 shares of AVI's common stock at an exercise price of $3.61 per share. During 2009, 2008 and 2007, we did not recognize any revenue from our relationship with Ercole.

External Project Funding

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

CHDI Foundation, Inc.

In November 2007, we entered into an agreement with CHDI, which provides us with up to $9.9 million in funding for the discovery and development of an antisense drug for the treatment of Huntington's disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's disease. If we grant a license to a third party to commercialize our Huntington's disease program, we and CHDI will evenly split the proceeds from the license until CHDI has recouped its funding together with a return determined at a predefined interest rate. Thereafter, we will keep the full amount of any additional proceeds. During 2009, 2008 and 2007, we recognized revenue of $1.7 million, $2.7 million and $329,000, respectively, from our relationship with CHDI.

Korea Institute of Toxicology

In March 2007, we entered an agreement with the Korea Institute of Toxicology, or KIT. Under the agreement, at our request, KIT will perform toxicology studies on our drugs at reduced preclinical costs in exchange for a nominal royalty. KIT has conducted toxicology and other IND-enabling studies for our ISIS-CRP_{Rx} program, thereby enabling us to initiate a Phase 1 safety study for ISIS-CRP_{Rx} in August 2008. Our relationship with KIT allows for the potential to perform toxicology studies on a number of our other drugs at a significantly reduced cost to us. We are only required to pay KIT when we engage them to perform studies for us.

Michael J. Fox Foundation

In July 2009, we were awarded a grant from the Michael J. Fox Foundation's Therapeutic Development Initiative, which provides us with funding for preclinical research to validate and evaluate a potential antisense target for the treatment of Parkinson's Disease. During 2009, we recognized revenue of $94,000 from our relationship with the Michael J. Fox Foundation.

ALS Association; The Ludwig Institute; Center for Neurological Studies; Muscular Dystrophy Association

In October 2005, we entered 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. The researchers from the Ludwig Institute and Center for Neurological Studies, through funding from the ALS Association and the Muscular Dystrophy Association, conducted IND-enabling preclinical studies of ISIS-$SOD1_{Rx}$. The ALS Association and the Muscular Dystrophy Association will provide funding to offset the costs of the Phase 1 study of ISIS-$SOD1_{Rx}$. Except for the funding provided by the ALS Association and the Muscular Dystrophy Association, we control and are responsible for funding the continued development of ISIS-$SOD1_{Rx}$.

Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We own or exclusively license more than 1,600 issued patents, which we believe 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 like AMI, Idera Pharmaceuticals, Inc., Integrated DNA Technologies, Inc., or IDT, Roche Molecular Systems, Silence Therapeutics plc., formerly Atugen AG, and Dharmacon, Inc., now a part of Thermo Fisher Scientific, Inc. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc., a wholly owned subsidiary of OSI Pharmaceuticals, Inc. To date, we have generated more than $355 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

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 patents and technology, including as it relates 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 it to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of RNase H, patents. In each of 2009 and 2007, we recognized revenue of $10,000 from our relationship with Idera, compared to none for 2008.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, we expanded this license agreement to allow us to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees in 2001 and will pay royalties on sales of the drugs utilizing the technology IDT licensed to us.

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

Abbott Molecular Inc.

In January 2008, we and our former subsidiary, Ibis Biosciences, entered into a Strategic Alliance Master Agreement and a Call Option Agreement with AMI. In 2008, AMI invested $40 million in Ibis and we granted AMI an exclusive call option to acquire from us all remaining Ibis capital stock. In December 2008, AMI exercised the call option and we, Ibis and AMI executed a stock purchase agreement. Under the stock purchase agreement, AMI purchased the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. AMI's initial investments totaling $40 million, along with the $175 million AMI paid at closing, resulted in a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, AMI will also pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products from the date of the acquisition closing through December 31, 2025. The earn out payments will equal 5 percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and 3 percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from 5 percent to as low as 2.5 percent and from 3 percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. As part of the acquisition, Ibis distributed to us, immediately prior to the closing, all uncommitted cash and cash equivalents held by Ibis as of the closing.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, now a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in milestone payments, and our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. During 2009, 2008 and 2007, because of our agreement with Drug Royalty Trust 3 as described below we did not recognize any revenue from our relationship with Eyetech.

Drug Royalty Trust 3

In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty Trust 3. To date, we have received a total of $23 million under this arrangement. We and Drug Royalty Trust 3 shared the royalty rights on Macugen from Eyetech through 2009. After 2009, we retain all royalties for Macugen. As a result, we will begin receiving royalties for Macugen in 2010. We retained all milestones payable to us by Eyetech under the license agreement. During 2009 and 2008, we did not recognize any revenue under this arrangement, compared to $7 million in 2007.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. During 2009, 2008 and 2007, we recognized revenue of $1.3 million, $1.2 million and $807,000, respectively, from our relationship with Roche Molecular Systems.

Regulus Collaborations

We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. We own 51 percent of Regulus and Alnylam owns the remaining 49 percent. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from a limited liability company to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing. We and Alnylam were the sole and equal investors in the financing.

GlaxoSmithKline

In April 2008, Regulus entered into a strategic alliance with GSK to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance utilizes Regulus' expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exercise its option earlier. After exercise of the option, GSK will have an exclusive license to drugs Regulus develops under each program for the relevant microRNA target for further development and commercialization on a worldwide basis. Regulus will have the right to further develop and commercialize any microRNA therapeutics which GSK chooses not to develop or commercialize.

Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. Regulus is eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In May 2009, Regulus received a $500,000 discovery milestone payment from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. In addition, Regulus would receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance. During 2009 and 2008, Regulus recognized revenue of $3.0 million and $1.9 million, respectively, related to Regulus' collaboration with GSK.

In February 2010, Regulus announced the establishment of a new worldwide strategic alliance with GSK to develop and commercialize microRNA therapeutics targeting miR-122 for the treatment of HCV infection. The new HCV alliance expands the ongoing GSK-Regulus immuno-inflammatory disease alliance formed in 2008. Under the terms of the new collaboration, Regulus will receive additional upfront and early stage milestone payments with the potential to earn more than $150 million in miR-122-related combined payments, and tiered royalties up to double digits on worldwide sales.

Under the terms of the HCV collaboration, Regulus will receive $8 million from GSK, including a $3 million license fee and a second $5 million note, guaranteed by Isis and Alnylam, that will convert into Regulus common stock in the future under certain specified circumstances. In addition, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestone payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

As part of the HCV collaboration, Regulus granted GSK a limited license to develop and commercialize the miR-122 antagonist SPC 3649, if GSK acquires rights to this compound. Regulus will receive development and regulatory milestones as well as royalties if GSK develops and commercializes SPC 3649.

Manufacturing

Drug Discovery and Development

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 mipomersen, 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 an approximately 28,704 square foot building in Carlsbad, California. In September 2005, as part of a sale and lease-back transaction, we entered into a lease for this building with an affiliate of BioMed Realty, L.P. The lease has an initial term of 15 years with an option to extend the lease for up to two five-year periods.

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

Regulus Therapeutics

Currently, Regulus only requires small quantities of drugs to conduct its drug discovery programs. We can satisfy Regulus' current demand using our existing internal resources. When Regulus identifies a clinical candidate, it will have to ensure that it has a manufacturer for its drugs.

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. We file applications, as appropriate, claiming products and processes. As of February 10, 2010, we owned or exclusively licensed more than 1,600 issued patents worldwide.

Isis Pharmaceuticals, Inc.

We own or control patents that provide exclusivity for particular products in development and patents that provide exclusivity to our core technology in the field of antisense more generally. Our core technology patents include claims to chemically modified oligonucleotides and antisense drug designs independent of specific therapeutic target, nucleic acid

sequence, or clinical indication. Other patents claim antisense compounds having nucleic acid sequences complementary to therapeutic target nucleic acids, independent of chemical modifications of the antisense compounds. Finally, we draw claims providing exclusivity for a particular product more narrowly to combine specific nucleic acid sequences and chemical modifications. We maintain our competitive advantage in the field of antisense technology by protecting our core platform technology and by creating multiple layers of patent protection for each of our potential drug products.

The most broadly-applicable Isis patents claim nucleoside modifications and oligonucleotides comprising the modified nucleosides that Isis incorporates into its antisense drugs to increase their therapeutic efficacy. Since nucleosides are the basic building blocks of antisense drugs and these claims are not limited to a particular oligonucleotide sequence or therapeutic target, they can reach oligonucleotides that utilize a wide range of antisense approaches, such as RNase H, RNAi, or splicing, for any number of clinical indications. Notably, claims of U.S. Patent No. 5,914,396, expiring in 2016, and 7,101,993, expiring in 2023, cover oligonucleotides having 2'-methoxyethoxy, or 2'-MOE, nucleosides, the chemical modification we use in all of our second generation antisense drugs that are currently in development. We have filed a wide array of patent applications drawn to nucleosides and oligonucleotides that are in the running for our new Generation 2.5 platform chemistry. To date, we have received three issued patents, US Patent No. 7,399,845 and 7,547,684 (each with an expiration of 2027), which cover some of the modified nucleotides that we are evaluating for our Generation 2.5 chemistry.

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 make oligonucleotides comprising them particularly suited for a particular cellular mechanism of action. For example, US Patent No. 7,015,315, or the '315 Patent, claims oligonucleotides comprising a region modified with 2'-O-alkyl substituents, such as 2'-MOE, and a region comprising deoxyribonucleosides. Oligonucleotides incorporating these motifs, sometimes referred to as chimeric compounds or gapmers, are designed to exploit the RNase H mechanism. Almost all of our drugs, including mipomersen, contain this gapmer antisense drug design motif. In fact, the '315 Patent covers each of our second generation antisense drugs until March of 2023. Similarly, US Patent Nos. 5,898,031, 6,107,094, 7,432,249, 7,432,250, and 7,629,321 (the Crooke Patents), cover oligonucleotides comprising methods and motifs useful for exploiting the RNAi pathway until June of 2016. We licensed the Crooke Patents to Alnylam for the development of double-stranded therapeutics and to Regulus for the development of microRNA-based therapeutics.

We also own more than 400 patents, worldwide, with claims to antisense oligonucleotides directed to particular therapeutically important targets or methods of achieving clinical endpoints using antisense oligonucleotides. Many of these patents include claims to any oligonucleotide that hybridizes to the particular target. For example, in 2008, we obtained US Patent No. 7,407,943, which is 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 mipomersen and potential future follow-on compounds. In March of 2009, claims to the specific antisense sequence and chemical composition of mipomersen issued in US Patent No. 7,511,131, which should protect mipomersen until at least 2023. 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.

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.

Regulus Therapeutics

Regulus has been granted exclusive licenses to both our and Alnylam's intellectual property for microRNA applications. This includes a portfolio of over 900 patents and patent applications, of which over 600 are issued, including our patents claiming chemical modification of oligonucleotides for therapeutic applications. In addition, Regulus has acquired rights to a large estate of patents and patent applications accumulated by both us and Alnylam in the field of microRNA therapeutics, including early fundamental patents in the field of microRNAs. Like the Isis portfolio, Regulus owns or controls patents directed to core technology, specific microRNA compounds, and methods of modulating microRNAs for several therapeutic indications. Regulus exclusively controls the therapeutic rights stemming from the discovery of more than 120 mammalian microRNAs by Dr. Thomas Tuschl. The first patent to issue from this patent

portfolio, U.S. Patent No. 7,232,806, includes claims to antisense compounds targeted to miR-122. Regulus also has non-exclusive access to additional novel microRNAs discovered by Dr. Thomas Tuschl. Regulus exclusively controls the patent portfolio that originated from Dr. Peter Sarnow's discovery that antagonism of miR-122 affects HCV replication. This patent portfolio has yielded U.S. Patent No. 7,307,067, which claims methods of inhibiting HCV replication in a cell with an oligonucleotide antagonist targeted to miR-122. These Regulus issued patents should protect therapeutic applications of miR-122 until at least September of 2022. Additionally Regulus owns or controls patent portfolios covering other therapeutic applications of microRNA compounds, such as cholesterol lowering and immune response modulation.

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 such products. State, local, and other authorities also regulate pharmaceutical manufacturing facilities and procedures.

In conjunction with obtaining approval of Vitravene, we successfully passed the manufacturing pre-approval inspection by the FDA and European regulatory authorities. Approval of each new drug, including mipomersen, will require a rigorous manufacturing pre-approval inspection by regulatory

authorities.

Competition

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

Employees

As of February 10, 2010, we employed approximately 250 people in all of our functions, excluding manufacturing and operations which employed approximately 50 people. In addition, our Regulus subsidiary employed 35 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 10, 2010:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D	64	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D	54	Director, Chief Operating Officer, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D	53	Senior Vice President, Antisense Research
Richard S. Geary, Ph.D	52	Senior Vice President, Development

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, Chief Financial Officer and Secretary

Ms. Parshall has served as a Director of Isis since September 2000. She was promoted to Chief Operating Officer in December 2007 and previously served as an Executive Vice President since December 1995. She has served as our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP (now Cooley Godward Kronish 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 serves on the Scientific Advisory Board of Keystone Symposia, a non-profit organization dedicated to connecting the scientific community for the benefit of society, and is an external member of the Scientific Advisory Board of Experimental Therapeutics Center in Singapore.

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

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

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 we or our partners fail to obtain regulatory approval for our drugs, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our

drugs, including mipomersen and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial drug product, Vitravene. We cannot guarantee that any of our other drugs, including mipomersen and ISIS 113715, will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

If the results of clinical testing indicate that any of our drugs under development 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 technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

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. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage NSCLC and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support a new drug application filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including mipomersen and ISIS 113715, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these and other drugs and our stock price could decline.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee the drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the Phase 2 results for mipomersen and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial 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 trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 or Phase 3 development programs for mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

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

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. Even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved drug product,

Vitravene, a treatment for CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- the cost and effectiveness of our drugs compared to other available therapies;
- the 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 use any products that we may develop.

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

If we successfully commercialize any of our drugs, we would be required 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 product costs. We may not be able to manufacture 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, which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

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

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged 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 products 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 develop treatments for the same diseases targeted by our own collaborative programs. 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.

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 trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that its board approves. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

We depend on third parties in the conduct of our clinical trials 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 in the conduct of our clinical trials for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for mipomersen. We rely heavily on these parties for successful execution of our clinical trials, 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 trials in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials 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 mipomersen.

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 product discovery and development require 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, 2009, we had an accumulated deficit of approximately $696.2 million and stockholders' equity of approximately $302.1 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 currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. We expect to 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 services, 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 product 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 products, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Our corporate partners are developing and/or funding, many of the drugs in our development pipeline, including Altair, ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, OncoGenex, and Teva. In addition, we have a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the disappointing results of the Phase 3 clinical trials, Eli Lilly and Company discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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 product development programs.

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

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

Once we have secured a collaborative arrangement to further develop and commercialize one of our development programs, such as our collaborations with Genzyme and Bristol-Myers Squibb, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator such as Genzyme or Bristol-Myers Squibb, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product 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 under development.

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.

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 trial, 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 investors' expectations, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in the first half of 2011. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

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 our ability to 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.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could 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 December 2006, the European Patent Office, or EPO, Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

If a third party claims that our products 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 applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. As of December 31, 2009, we had cash, cash equivalents and short-term investments equal to $574.3 million. If we do not meet our goals to commercialize our products, 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:

- 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 trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their 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 decided to terminate 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, drugs or products.

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 trials 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, 2009, the market price of our common stock ranged from $9.77 to $18.81 per share. On February 22, 2010, the closing price of our common stock on The Nasdaq Global Select Market was $9.03. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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. These materials and various wastes resulting from their use are stored 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 type 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. In the event 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, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a separate 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 in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 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 also have implemented 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. These provisions, as well as Delaware 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. 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 subordinated 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 mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually agree 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.

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 registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^{5}/_{8}$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the 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 will incur additional expenses and will suffer a diversion of management's time. 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 Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these

events on our business and the severity of the economic crisis is uncertain. It is possible that the crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 10, 2010, we occupied approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business terminate in December 2011. The lease on the building we primarily use for our drug development manufacturing expires in 2020 and has two five-year options to extend the lease.

Item 3. Legal Proceedings

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery remains in its early stage. As such, we have no basis on which to predict or record a loss related to this claim as of December 31, 2009. We will continue to represent and defend Ibis Biosciences in this matter.

Item 4. Reserved

PART II

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

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

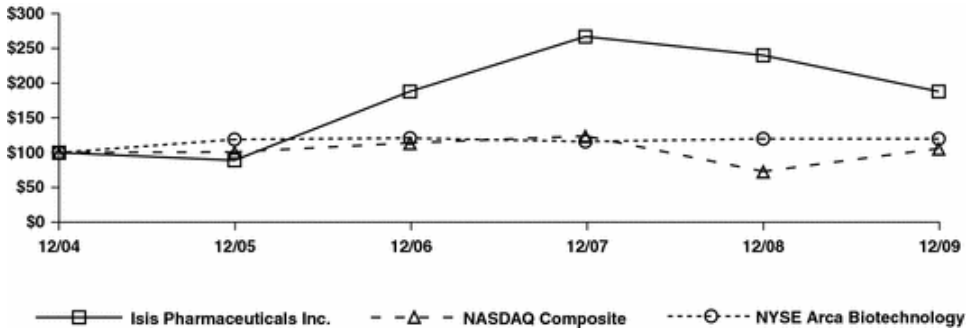
	HIGH	LOW

2009		
First Quarter	$ 15.67	$ 11.65
Second Quarter	$ 17.70	$ 13.13
Third Quarter	$ 18.81	$ 14.46
Fourth Quarter	$ 14.59	$ 9.77
2008		
First Quarter	$ 20.15	$ 12.70
Second Quarter	$ 17.77	$ 10.91
Third Quarter	$ 19.29	$ 13.42
Fourth Quarter	$ 16.93	$ 9.90

As of February 22, 2010, there were approximately 922 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, 2004 in our common stock, the NASDAQ Composite Index (total return) and the NYSE Arca Biotechnology Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



	Dec-04	Dec-05	Dec-06	Dec-07	Dec-08	Dec-09
Isis Pharmaceuticals, Inc.	$ 100	$ 89	$ 188	$ 267	$ 240	$ 188
NASDAQ Composite Index	$ 100	$ 101	$ 114	$ 124	$ 73	$ 106
NYSE Arca Biotechnology Index	$ 100	$ 119	$ 121	$ 116	$ 120	$ 120

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

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

	Years Ended December 31,				
	2009	2008	2007	2006	2005
Consolidated Statement of Operations Data:					
Revenue(1)	$ 121,600	$ 107,190	$ 58,344	$ 14,859	$ 28,340
Research and development expenses(1)	$ 134,623	$ 106,439	$ 78,204	$ 69,411	$ 72,309
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)(2)(3)(4)	$ (30,562)	$ (9,785)	$ (10,264)	$ (43,003)	$ (74,036)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(3)(4)	$ 155,066	$ (18,172)	$ (141,604)	$ (45,903)	$ (72,401)
Basic and diluted net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)(2)(3)(4)	$ (0.31)	$ (0.10)	$ (0.12)	$ (0.58)	$ (1.18)
Basic and diluted net income (loss) per share attributable to Isis Pharmaceuticals, Inc. common stockholders(3)(4)	$ 1.58	$ (0.19)	$ (1.69)	$ (0.62)	$ (1.15)
Shares used in computing basic and diluted net income (loss) per share	98,109	94,566	83,739	74,308	62,877

	As of December 31,				
	2009	2008	2007	2006	2005
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments(5)	$ 574,312	$ 490,998	$ 193,719	$ 193,333	$ 94,389
Working capital(5)	$ 484,682	$ 393,685	$ 147,669	$ 181,064	$ 82,065
Total assets(6)	$ 657,184	$ 572,776	$ 257,216	$ 255,907	$ 166,373
Long-term debt and other obligations, less current	$ 243,675	$ 300,697	$ 135,426	$ 132,866	$ 139,915

portion(5)(6)					
Accumulated deficit(6)	$ (696,150)	$ (851,216)	$ (833,044)	$ (816,751)	$ (770,848)
Noncontrolling interest in Symphony GenIsis, Inc.	$ —	$ —	$ —	$ 29,339	$ —
Noncontrolling interest in Regulus Therapeutics Inc.	$ 10,343	$ 4,737	$ 9,371	$ —	$ —
Noncontrolling interest in Ibis Biosciences, Inc.	$ —	$ 32,419	$ —	$ —	$ —
Stockholders' equity(6)	$ 302,065	$ 147,380	$ 59,585	$ 97,902	$ 2,665

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

(2) Our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders and our net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders calculation include charges (benefit) related to restructuring activities of ($536,000) and $7.0 million in 2006 and 2005, respectively.

(3) Our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders; and the related per share information include a change of $125.3 million relating to excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc. in 2007.

(4) We have adjusted our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders; net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders; and the related per share information in 2008 and 2007 to reflect the required retroactive adoption of accounting standards. See Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements for additional details.

(5) As a result of the sale of Ibis to AMI, we have adjusted our cash, cash equivalents and short-term investments balance; working capital; and long-term debt and other obligations balance at December 31, 2008 and our working capital at December 31, 2007 to reflect Ibis' assets and liabilities as assets and liabilities from discontinued operations.

(6) We have adjusted our total assets; long-term debt and other obligations; accumulated deficit; and stockholders' equity at December 31, 2008 and 2007 and our stockholders' equity at December 31, 2006 to reflect the required retroactive adoption of accounting standards. See Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements for additional details.

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

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Bristol-Myers Squibb, Genzyme and Eli Lilly and Company. Additionally, we have created a consortium of smaller companies that can

broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as Ibis Biosciences, a subsidiary of ours that we sold in early 2009 to AMI. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated more than $355 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. Our clinical experience with mipomersen demonstrates that antisense drugs work in man. We and Genzyme reported positive data from two Phase 3 studies in patients with FH. Both studies met their primary and secondary endpoints with reductions in LDL-C and other generally accepted risk factors for cardiovascular disease. These data are consistent with our observations of mipomersen in earlier clinical studies and support the profile of the drug as a novel treatment to reduce LDL-C in patients with high cholesterol, and at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform and increased the value of our drugs.

Since 2007, our partnerships have generated an aggregate of more than $750 million in payments from licensing fees, equity purchase payments and milestone payments. In addition, for our partnered drugs we have the potential to earn approximately $2.5 billion in future milestone payments. We also will

share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Business Segments

Prior to AMI's acquisition of our Ibis Biosciences business, we focused on three segments. We currently focus our business on two principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 22 drugs in development. Our partners are licensed to develop, with our support, 12 of these 22 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, 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 diagnostic tool for disease characterization.

Beginning in the first quarter of 2010, as a result of a new accounting standard, we will no longer include Regulus' revenue and operating expenses in our operating results and will no longer include Regulus' cash in our cash balance, which at December 31, 2009 was $30.7 million. See Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements for a more detailed explanation of this change.

Ibis Biosciences, Inc. In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total purchase price of $215 million. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. Early in 2009, AMI completed the acquisition of Ibis and we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis products that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5 percent of net sales over $140 million through net sales of $2.1 billion and 3 percent of net sales over $2.1 billion, with the percentages subject to reduction in specified circumstances.

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for 2009 and all prior periods in our financial statements separately as discontinued operations and therefore Ibis is no longer included in our segment reporting.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to 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 the audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment.

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

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in available-for-sale securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments;
- Determination of the fair value of convertible debt without the conversion feature; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

We often enter into collaborations under which we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to estimate our period of performance when the agreements we enter into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Bristol-Myers Squibb, Genzyme, Eli Lilly and Company, OncoGenex and Pfizer. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. 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. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable, the amounts are not refundable and we have no future performance obligations related to the achievement of the milestone. In April 2008, Bristol-Myers Squibb selected a development candidate, BMS-PCSK9$_{RX}$, for which we earned a $2 million milestone payment. In 2009, we received a $1 million milestone payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, because Achaogen filed an IND for its aminoglycoside drug, ACHN-490. Because realization of the these securities is uncertain, we recorded a full valuation allowance and recognized $500,000 of this milestone in the first quarter of 2009.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate fair value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

As part of our Genzyme strategic alliance, in February 2008 Genzyme made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represented value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan. See further discussion about our collaboration with Genzyme in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

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

Valuation of Investments in Marketable Securities

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

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our majority owned subsidiary, which we consolidate with our financial results. 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. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. When 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 2009, we recognized a $2.1 million gain on investments consisting of a $2.5 million gain when we sold all of the common stock of OncoGenex that we owned and a $574,000 gain that we realized on our available-for-sale securities offset by a $1.0 million valuation allowance we recorded related to our investment in Altair. Because realization of our Altair investment is uncertain we recorded a full valuation allowance. See further discussion about our investment in Altair in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements. During 2008, we recognized a $965,000 loss on investments consisting of a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex and a $198,000 gain that we realized on our available-for-sale securities. See further discussion about our investment in OncoGenex in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements. During 2007, we sold

the remainder of our equity securities of Alnylam that we owned resulting in a realized gain of $3.5 million. We determined that there were no other-than-temporary declines in value of our investments in 2009 and 2007.

Valuation of Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. 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 will issue an application and the scope of our issued patents.

We recorded a charge of $696,000, $1.9 million and $887,000 for the years ended December 31, 2009, 2008 and 2007, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values except in 2008 when the charge primarily related to the assignment of patents to certain of our partners.

Valuation of Inventory

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

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

We record a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net 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. When and if circumstances warrant, we will assess the likelihood that we will more likely than not recover our net deferred tax assets from future taxable income and record an appropriate reversal to the valuation allowance.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Regulus subsidiary based on the segregation of revenues and expenses we use for management's assessment of operating performance and operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments. We have not made material changes to our allocation methodologies since we began reporting segment financial information and results. Different assumptions or allocation methods could result in materially different results by segment. Prior to completing the sale of Ibis to AMI, we reported Ibis as a separate segment. As a result of the sale, we have presented the operating results of Ibis separately as discontinued operations for all periods presented in our consolidated financial statements.

Convertible debt

On January 1, 2009, we adopted an accounting standard, which requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our

nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$ percent convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our consolidated financial statements. For additional information, see Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

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 in effect, the associated non-cash interest expense. The carrying amount of the liability component is determined by measuring the fair value of a similar debt instrument that does not have the conversion feature. If no similar debt instrument exists, estimates of fair value are primarily determined using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

Stock-Based Compensation

We utilize the Black-Scholes model and assumptions discussed in Note 5, *Stockholders' Equity*, in the Notes to the Consolidated Financial Statements, for estimating the fair value of the stock-based awards we grant. We recognize compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. We base our risk-free interest rate assumption on observed interest rates appropriate for the term of our employee stock options and our Employee Stock Purchase Plan, or ESPP. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model. The expected term of stock options granted represents the period of time that they are expected to be outstanding.

For our 2002 Non-Employee Directors' Stock Option Plan and for stock options granted on or after January 1, 2008 for our employee stock option plans, we estimate the expected term of options granted based on historical exercise patterns. For the stock options granted prior to January 1, 2008 for our employee stock option plans, we determine the estimated expected term as a derived output of the simplified method. We estimate forfeitures based on historical experience. There were no material changes to our estimated forfeitures for 2009, 2008 and 2007.

We account for stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, by estimating their fair value. Until the stock option is vested, we remeasure the fair value at each reporting period. We recognize the expense over the period of time we require the non-employee to perform services.

As of December 31, 2009, total unrecognized compensation cost related to non-vested stock-based compensation plans was $11.0 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.

Results of Operations

Years Ended December 31, 2009 and December 31, 2008

Revenue

Total revenue for the year ended December 31, 2009 was $121.6 million, compared to $107.2 million for 2008. The increase was primarily due to an increase in revenue from our collaboration with Genzyme and the $10 million sublicensing revenue we earned in 2009 from OncoGenex when OncoGenex licensed OGX-011 to Teva offset, in part by a decrease in revenue from our collaboration with OMJP. In August 2009, we finished amortizing the revenue associated with the $50 million upfront payment we received from OMJP in 2007 resulting in a decrease in revenue in 2009 compared to 2008. As part of our strategic relationship with Genzyme, in the first quarter of 2008 Genzyme purchased $150 million of our common stock at $30 per share and in the second quarter of 2008 paid us a license fee of $175 million. We are amortizing the premium on the stock of $100 million, calculated using a Black-Scholes option valuation model, and the license fee ratably into revenue through June 2012, which represents the end of our performance obligation based on the current research and development plan.

Collaborations with Alnylam, Bristol-Myers Squibb, Genzyme and Regulus' strategic alliance with GSK include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received and from research and development funding. Assuming no new transactions, our revenue will decrease when the $15 million upfront payment we received from Bristol-Myers Squibb in May 2007 is fully amortized in the second quarter of 2010.

Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, in 2009, we earned $11 million of sublicensing revenue from OncoGenex and Alnylam, while in 2008, we earned $6 million in sublicensing revenue from Alnylam and ATL.

The following table sets forth information on our revenue by segment (in thousands):

	Year Ended December 31,	
	2009	2008
Drug Discovery and Development:		
Research and development revenue	$ 105,118	$ 96,743

Licensing and royalty revenue	13,469	8,337
	$ 118,587	$ 105,080
Regulus Therapeutics:		
Research and development revenue	$ 3,013	$ 2,110
	$ 3,013	$ 2,110
Total revenue:		
Research and development revenue	$ 108,131	$ 98,853
Licensing and royalty revenue	13,469	8,337
	$ 121,600	$ 107,190

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2009 was $105.1 million, compared to $96.7 million for 2008. The increase was primarily due to the increase in revenue from our collaboration with Genzyme offset, in part by the decrease in revenue from our collaboration with OMJP that we describe above.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2009 was $13.5 million, compared to $8.3 million for 2008. The revenue in 2009 primarily consisted of the $10 million sublicensing revenue we earned from OncoGenex when OncoGenex licensed OGX-011 to Teva and the $1 million sublicensing revenue we earned from Alnylam when Alnylam entered into a transaction with Cubist Pharmaceuticals, Inc. that included technology we had licensed to Alnylam, compared to revenue in 2008 that primarily consisted of the $4.6 million and $1.4 million sublicensing revenue we earned in 2008 from Alnylam and ATL, respectively.

Regulus Therapeutics

Regulus' revenue for the year ended December 31, 2009 was $3.0 million, compared to $2.1 million for 2008. The increase was primarily related to revenue from Regulus' collaboration with GSK including the $500,000 discovery milestone payment that Regulus earned from GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which Regulus began amortizing into revenue in the second quarter of 2008 and will continue to amortize over Regulus' six year period of performance under the agreement.

Beginning in the first quarter of 2010, as a result of a new accounting standard, we will no longer include Regulus' revenue in our revenue. Instead we will include our share of Regulus' revenue along with our share of the rest of their operating results on a separate line in the other income section of our Statement of Operations called "Equity in loss of Regulus Therapeutics Inc." See Note 1, *Organization and Significant Accounting Policies*, for a more detailed explanation of this change.

Operating Expenses

Operating expenses for the year ended December 31, 2009 were $149.1 million, compared to $120.3 million for 2008. The higher expenses in 2009 compared to 2008 were primarily due to the expansion of our clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas.

Our operating expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2009	2008
Drug Discovery and Development	$ 137,402	$ 110,219
Regulus Therapeutics	11,736	10,031
Total operating expenses	$ 149,138	$ 120,250

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

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs. In addition, our research and development expenses include costs associated with the research activities Regulus is conducting to advance its microRNA technology.

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

	Year Ended December 31,	
	2009	2008

Research and development expenses	$ 123,646	$ 95,861
Non-cash compensation expense related to stock options	10,977	10,578
Total research and development	$ 134,623	$ 106,439

Our research and development expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2009	2008
Drug Discovery and Development	$ 125,642	$ 99,259
Regulus Therapeutics	8,981	7,180
Total research and development	$ 134,623	$ 106,439

For the year ended December 31, 2009, we incurred total research and development expenses of $123.6 million, compared to $95.9 million for 2008, both amounts exclude non-cash compensation expense related to stock options. We attribute the increase in expenses to the expansion of our clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas. We discuss expenses related to Regulus in a separate section below.

Drug Discovery & Development

Antisense Drug Discovery

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

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipeline. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as 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,	
	2009	2008
Antisense drug discovery	$ 27,535	$ 20,311
Non-cash compensation expense related to stock options	3,067	2,321
Total antisense drug discovery	$ 30,602	$ 22,632

Antisense drug discovery costs were $27.5 million for the year ended December 31, 2009, compared to $20.3 million for 2008, both amounts exclude non-cash compensation expense related to stock options. The higher expenses in 2009 were primarily due to increased activity levels related to our planned investment to fill our pipeline and additional spending to enhance our platform technology and to support collaborative research efforts for which we earn revenue. These activities resulted in an increase in personnel, laboratory supplies and research services provided by third parties in 2009.

Antisense Drug Development

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

	Year Ended December 31,	
	2009	2008
Mipomersen	$ 26,909	$ 16,640
Other antisense development products	17,472	15,919
Development overhead costs	4,253	3,882
Non-cash compensation expense related to stock options	3,578	3,366
Total antisense drug development	$ 52,212	$ 39,807

Antisense drug development expenditures were $48.6 million for the year ended December 31, 2009 compared to $36.4 million for 2008, both amounts exclude non-cash compensation expense related to stock options. We attribute the increase primarily to the broad Phase 3 program for mipomersen, and increases in our other cardiovascular development projects. Development overhead costs were $4.3 million for the year ended December 31, 2009, compared to $3.9 million for 2008. The increase in overhead costs was a result of the additional resources needed to support the expansion of our clinical development programs. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials.

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 where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated

resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 12 of our 22 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme

will share development costs equally. Our initial development funding commitment and the shared funding will end when the program 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,	
	2009	2008
Manufacturing and operations	$ 14,415	$ 11,445
Non-cash compensation expense related to stock options	1,440	1,096
Total manufacturing and operations	$ 15,855	$ 12,541

Manufacturing and operations expenses for the year ended December 31, 2009 were $14.4 million, compared to $11.4 million for 2008, both amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in depreciation relating to upgrades made to our manufacturing facility, which were completed in the second quarter of 2009. Also contributing to the increase was an increase in manufacturing supplies and personnel costs to support our expanded clinical development programs including our broad Phase 3 program for mipomersen.

R&D Support

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

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

	Year Ended December 31,	
	2009	2008
Personnel costs	$ 7,859	$ 6,097
Occupancy	7,230	6,619
Depreciation and amortization	6,379	5,952
Insurance	903	910
Other	2,739	1,559
Non-cash compensation expense related to stock options	3,058	2,291
Total R&D support costs	$ 28,168	$ 23,428

R&D support costs for the year ended December 31, 2009 were $25.1 million, compared to $21.1 million for 2008, both amounts exclude non-cash compensation expense related to stock options. The increase was primarily a result of an increase in personnel costs in 2009, lease modification fees paid in September 2009 and $750,000 we received from Ercole in March 2008 as repayment of a convertible note that we had previously expensed.

Our R&D support costs by segment were as follows (in thousands):

	Year Ended December 31,	
	2009	2008
Drug Discovery and Development	$ 26,974	$ 23,428
Regulus Therapeutics	1,194	—
Total R&D support costs	$ 28,168	$ 23,428

As part of Regulus' conversion from a limited liability company to a C-Corporation in January 2009, we began providing Regulus research and development and general and administrative services under the terms of a services agreement. Under the terms of the services agreement, we allocate a portion of our R&D support costs to Regulus and include this allocation in Regulus' research and development expenses.

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, finance and Regulus' general and administrative expenses. 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,	
	2009	2008
General and administrative expenses	$ 12,107	$ 11,103
Non-cash compensation expense related to stock options	2,408	2,708
Total general and administrative	$ 14,515	$ 13,811

Our general and administrative expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2009	2008
Drug Discovery and Development	$ 11,760	$ 10,960
Regulus Therapeutics	2,755	2,851
Total general and administrative	$ 14,515	$ 13,811

General and administrative expenses for the year ended December 31, 2009 were $12.1 million, compared to $11.1 million for 2008, both amounts exclude non-cash compensation expense related to stock options. The increase was primarily due to an increase in tax consulting expenses associated with our taxable income in 2009 and legal fees associated with our litigation with Bruker Daltonics Inc. We discuss expenses related to Regulus in a separate section below.

Regulus Therapeutics

The following table sets forth information on Regulus' operating expenses (in thousands):

	Year Ended December 31,	
	2009	2008
Research and development expenses	$ 9,147	$ 5,674
General and administrative expenses	2,490	1,943
Non-cash compensation expense related to stock options	99	2,414
Total Regulus' operating expenses	$ 11,736	$ 10,031

Operating expenses for Regulus were $11.6 million for the year ended December 31, 2009, compared to $7.6 million in 2008, both amounts exclude non-cash compensation expense related to stock options. The increase was primarily related to Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration, which began in April 2008. With the strategic alliance with GSK, we anticipate that Regulus' expenses will increase going forward as Regulus advances its research and development activities.

Non-cash compensation expense related to stock options for the year ended December 31, 2009 was $99,000, compared to $2.4 million for 2008. The decrease was a result of the modifications made in 2009 to Alnylam's and our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. For additional information, see Note 5, *Stockholders' Equity,* in the Notes to the Consolidated Financial Statements.

Beginning in the first quarter of 2010, as a result of a new accounting standard, we will no longer include Regulus' operating expenses in our operating expenses. Instead we will include our share of Regulus' operating expenses along with our share of the rest of their operating results on a separate line in the other income section of our Statement of Operations called "Equity in loss of Regulus Therapeutics Inc." See Note 1, *Organization and Significant Accounting Policies*, for a more detailed explanation of this change.

Investment Income

Investment income for the year ended December 31, 2009 totaled $6.4 million, compared to $11.3 million for 2008. The decrease in investment income was primarily due to the lower average returns on our investments resulting from the current market conditions offset by a significantly higher average cash balance in 2009.

Interest Expense

Interest expense for the year ended December 31, 2009 totaled $12.7 million, compared to $11.8 million for 2008. In 2009, we adopted the accounting standard related to our 2½% convertible notes and retroactively applied it to 2008. As a result of adopting the standard, the amount of interest expense we recorded in our statement of operations for the year ended December 31, 2009 increased by $6.8 million, compared to an increase of $6.2 million for 2008. For additional information, see Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements. The increase in interest expense was also due to the effect of a higher average debt balance in 2009 compared to 2008 primarily related to our equipment financing arrangement.

Gain (Loss) on Investments, net

Gain on investments for the year ended December 31, 2009 was $2.1 million, compared to a net loss on investments of $965,000 in 2008. The net gain on investments in 2009 reflected a $2.5 million gain when we sold all of the common stock of OncoGenex that we owned and a $574,000 gain that we realized on our available-for-sale securities offset by a $1.0 million valuation allowance we recorded in November 2009 related to our investment in Altair. Because realization of our Altair investment is uncertain we recorded a full valuation allowance. See further discussion about our investment in Altair in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements. The net loss on investments in 2008 reflected a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex partly offset by gains on the sales of our available-for-sale securities.

Income Tax Expense

Even though we finished 2009 with a net loss from continuing operations, we had taxable income, which is primarily a result of the significant upfront payments that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI in early 2009. We recorded income tax expense of $3.2 million in 2009 as part of our financial results from continuing operations.

Net loss from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Year Ended December 31,	
	2009	2008
Net loss from continuing operations, including income tax expense	$ (34,956)	$ (14,519)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	4,394	4,734
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (30,562)	$ (9,785)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2009 was $30.6 million, compared to $9.8 million for 2008. Net loss from continuing operations in 2009 was higher than 2008 primarily due to the increase in operating expenses, the decrease in investment income and the income tax expense recognized in 2009 offset by the increase in revenue and the net gain on investments, all of which we discuss above.

Net Income (Loss) from Discontinued Operations

Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation on our financial statements. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations, net of tax, for the year ended December 31, 2009 was $185.6 million, compared to net loss from discontinued operations of $8.4 million for 2008. Net income from discontinued operations for 2009 primarily consisted of the $202.5 million gain less $16.8 million of income taxes.

Net Income (Loss) and Net Income (Loss) Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net income attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2009 was $155.1 million, compared to a net loss of $18.2 million for 2008. Basic and diluted net income per share for the year ended December 31, 2009 was $1.58 per share, compared to basic and diluted net loss of $0.19 per share for 2008. The improvement in our net income and net income per share in 2009 compared to 2008 was primarily due to the gain we recognized when we sold Ibis to AMI.

Net Operating Loss Carryforward

At December 31, 2009, we had federal, California and foreign tax net operating loss carryforwards of approximately $232.1 million, $190.5 million and $1.1 million, respectively. We also had federal and California research credit carryforwards of approximately $27.4 million and $8.2 million, respectively. Our federal and California tax loss carryforwards expire at various dates starting in 2014, unless previously utilized. Our foreign tax losses may be carried forward indefinitely and used to offset future taxable income, provided there is no substantial change in ownership. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to “change of ownership” provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Results of Operations

Years Ended December 31, 2008 and December 31, 2007

Revenue

Total revenue for the year ended December 31, 2008 was $107.2 million, compared to $58.3 million for 2007. The significant increase in 2008 revenue over 2007 was primarily a result of our collaboration with Genzyme as discussed in the current year Results of Operations section.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2008 was $96.7 million, compared to $22.2 million for 2007. The increase was primarily due to revenue from our collaborations with Bristol-Myers Squibb, OMJP and Genzyme.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2008 was $8.3 million, compared to $36.0 million for 2007. Licensing and royalty revenue in 2007 was higher primarily due to the $26.5 million licensing revenue that we earned from Alnylam in the third quarter of 2007.

Regulus Therapeutics

Regulus' revenue for the year ended December 31, 2008 was $2.1 million, compared to $119,000 for 2007. The increase was primarily due to revenue from its collaboration with GSK as discussed in the current year Results of Operations section.

Operating Expenses

Operating expenses for the year ended December 31, 2008 were $120.3 million, compared to $91.3 million for 2007. The higher expenses in 2008 compared to 2007 were primarily due to the expansion of our clinical development programs, including additional expenses associated with the development of mipomersen, increased activity levels related to our planned investment to fill our pipeline, and increased expenses related to manufacturing drug supplies for our corporate partners and our internal drug development programs. Also contributing to the increase in operating expenses was an increase of $7.0 million, excluding non-cash compensation expense related to stock options, in expenses associated with Regulus.

Furthermore, an increase in non-cash compensation expense related to stock options contributed to the increase in operating expenses. Non-cash compensation expense related to stock options was $13.3 million for the year ended December 31, 2008 compared to $8.3 million for 2007, primarily reflecting the increase in our stock price from 2007 to 2008.

Our operating expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2008	2007
Drug Discovery and Development	$ 99,345	$ 82,353
Regulus Therapeutics	7,619	612
Non-cash compensation expense related to stock options	13,286	8,298
Total operating expenses	$ 120,250	$ 91,263

Research and Development Expenses

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

	Year Ended December 31,	
	2008	2007
Research and development expenses	$ 95,861	$ 71,459
Non-cash compensation expense related to stock options	10,578	6,745
Total research and development	$ 106,439	$ 78,204

For the year ended December 31, 2008, we incurred total research and development expenses, excluding stock compensation, of $95.9 million, compared to $71.5 million for 2007. We attribute the increase in expenses to the expansion of our key programs and Regulus' research activities. We discuss expenses related to Regulus in a separate section below.

Drug Discovery & Development

Antisense Drug Discovery

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

	Year Ended December 31,	
	2008	2007
Antisense drug discovery	$ 20,311	$ 14,847
Non-cash compensation expense related to stock options	2,321	1,733
Total antisense drug discovery	$ 22,632	$ 16,580

Antisense drug discovery costs, excluding non-cash compensation expense, were $20.3 million for the year ended December 31, 2008, compared to $14.8 million for 2007. The higher expenses in 2008 compared to 2007 were primarily due to increased activity levels related to our planned investment to fill our pipeline and additional spending to support collaborative research efforts, which required an increase in personnel and laboratory supplies.

Antisense Drug Development

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

	Year Ended December 31,	
	2008	2007
Mipomersen	$ 16,640	$ 12,237
Other antisense development products	15,919	12,494
Development overhead costs	3,882	5,700
Non-cash compensation expense related to stock options	3,366	2,731
Total antisense drug development	$ 39,807	$ 33,162

Antisense drug development expenditures, excluding non-cash compensation expense, were $36.4 million for the year ended December 31, 2008 compared to $30.4 million for 2007. We attribute the increase primarily to the development of mipomersen, including the Phase 3 program, and increases in our metabolic disease development projects. Development overhead costs were $3.9 million for the year ended December 31, 2008, compared to $5.7 million for 2007. The decrease in overhead costs was primarily a result of people shifting the hours they worked from non-project specific activities to specific projects related to the development of our drugs.

Manufacturing and Operations

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

	Year Ended December 31,	
	2008	2007
Manufacturing and operations	$ 11,445	$ 7,080
Non-cash compensation expense related to stock options	1,096	596
Total manufacturing and operations	$ 12,541	$ 7,676

Manufacturing and operations expenses, excluding non-cash compensation expense, for the year ended December 31, 2008 were $11.4 million, compared to $7.1 million for 2007. The increase in expense was primarily due to the costs associated with an increase in the manufacturing of drug supplies for our corporate partners and our internal drug development programs.

R&D Support

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

	Year Ended December 31,	
	2008	2007
Personnel costs	$ 6,097	$ 5,387
Occupancy	6,619	6,056
Depreciation and amortization	5,952	4,987
Insurance	910	960
Other	1,559	1,711
Non-cash compensation expense related to stock options	2,291	1,685
Total R&D support costs	$ 23,428	$ 20,786

R&D support costs, excluding non-cash compensation expense, for the year ended December 31, 2008 were $21.1 million, compared to $19.1 million for 2007. The increase in 2008 compared to 2007 was primarily a result of the additional expenses necessary to support the continued development of our key programs and an increase in the non-cash charges for patents assigned to certain of our partners, offset by the $750,000 we received from Ercole in March 2008 as repayment of a convertible note that we had previously expensed.

General and Administrative Expenses

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

	Year Ended December 31,	
	2008	2007
General and administrative expenses	$ 11,103	$ 11,506
Non-cash compensation expense related to stock options	2,708	1,553
Total general and administrative	$ 13,811	$ 13,059

General and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2008 were $11.1 million, compared to $11.5 million for 2007. The decrease was primarily the result of higher external legal fees incurred in 2007 in connection with our arbitration proceeding with Idera, which ended in January 2008 when we prevailed in the matter and higher personnel costs in 2007 offset by the increase in Regulus' general and administrative expenses in 2008. We discuss expenses related to Regulus in a separate section below.

Regulus Therapeutics

The following table sets forth information on Regulus' operating expenses (in thousands):

	Year Ended December 31,	
	2008	2007
Research and development expenses	$ 5,674	$ 596
General and administrative expenses	1,943	16
Non-cash compensation expense related to stock options	2,414	412
Total Regulus' operating expenses	$ 10,031	$ 1,024

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $7.6 million for the year ended December 31, 2008 compared to $612,000 in 2007. Regulus began its operations in September 2007, therefore its 2007 operating expenses only reflect four months of activity compared to the entire year in 2008. Also contributing to the increase in its operating expenses from 2007 to 2008 were the research and development activities associated with its strategic alliance with GSK, which began in April 2008.

Investment Income

Investment income for the year ended December 31, 2008 totaled $11.3 million, compared to $11.4 million for 2007. The slight decrease in investment income was primarily due to our lower average returns on our investments resulting from the current market conditions offset by a higher average cash balance in 2008 compared to 2007 as a result of the proceeds we received from Genzyme of $325 million, from AMI of $40.5 million and from GSK of $20 million.

Interest Expense

Interest expense for the year ended December 31, 2008 totaled $11.8 million, compared to $12.9 million for 2007. The decrease in interest expense was due to the effect of a lower average debt balance in 2008 compared to 2007 primarily related to the fact that a portion of our old $5^1/_2$ percent notes was outstanding until we repaid the remaining balance in May 2007.

Gain (Loss) on Investments, net

Net loss on investments for the year ended December 31, 2008 was $965,000, reflecting a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex partly offset by gains on the sales of our available-for-sale securities. Gain on investments for the year ended December 31, 2007 was $3.5 million, reflecting a gain realized on the sale of the remaining equity securities of Alnylam that we owned.

Loss on Early Retirement of Debt

Loss on early retirement of debt for the year ended December 31, 2007 was $3.2 million, reflecting the early extinguishment of our $5^1/_2$ percent convertible subordinated notes in the first half of 2007. We did not recognize any loss on early retirement of debt in 2008.

Net Loss from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Year Ended December 31,	
	2008	2007
Net loss from continuing operations, including income tax expense	$ (14,519)	$ (34,050)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	4,734	629
Net loss attributable to noncontrolling interest in Symphony GenIsis, Inc.	—	23,157
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,785)	$ (10,264)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2008 was $9.8 million, compared to $10.3 million for 2008. The decrease in net loss from continuing operations was a result of a decrease in loss from operations in 2008 offset by a benefit of $23.2 million we recognized in 2007 for the loss attributed to noncontrolling interest in Symphony GenIsis, related to our collaboration with Symphony GenIsis. Additionally, we recognized a benefit of $4.7 million and $629,000 for the loss attributed to noncontrolling interest in Regulus for the years ended December 31, 2008 and 2007, respectively.

Net Loss from Discontinued Operations

In 2008, AMI purchased approximately 18.6 percent of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement. Under this agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009.

Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation on our financial statements. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net loss from discontinued operations for the year ended December 31, 2008 was $8.4 million compared to $6.0 million for 2007. The increase in net loss from discontinued operations in 2008 compared to 2007 primarily relates to an increase in expenses to support the growth of Ibis' commercial business including selling and support costs for the Ibis T5000 Biosensor System and the cost to achieve milestones as part of the AMI transaction partly offset by the gain recognized for the revaluation of the subscription right and call option we granted to AMI and a benefit of $2.1 million for the loss attributed to noncontrolling interest in Ibis for 2008.

Net Loss and Net Loss Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2008 was $18.2 million compared to $141.6 million for 2007. Basic and diluted net loss per share for the year ended December 31, 2008 was $0.19 per share, compared to $1.69 per share for 2007, of which $1.50 per share attributable to the purchase of Symphony GenIsis. In 2007, we purchased the equity of Symphony GenIsis. The $125.3 million on our Consolidated Statement of Operations in the line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend paid to the previous owners of Symphony GenIsis. This deemed dividend only impacts our net loss attributable to Isis Pharmaceuticals, Inc. common stockholders and our net loss per share calculations for 2007 and does not affect our net loss from continuing operations or discontinued operations.

Net Operating Loss Carryforward

At December 31, 2008, we had federal, California and foreign tax net operating loss carryforwards of approximately $591.1 million, $180.6 million and $1.1 million, respectively. We also had federal and California research credit carryforwards of approximately $31.3 million and $22.2 million, respectively. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal and California tax loss

carryforwards will continue to expire in 2008 and 2013, respectively, unless previously utilized. Our foreign tax losses may be carried forward indefinitely and used to offset future taxable income, provided there is no substantial change in ownership. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty 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, 2009, we have earned approximately $818.7 million 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, 2009, we have raised net proceeds of approximately $816.1 million from the sale of our equity securities and we have borrowed approximately $562.2 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2009, we had cash, cash equivalents and short-term investments of $574.3 million, which does not include the $10 million we received from OncoGenex in January 2010 for the sublicensing revenue we earned in December 2009, and stockholders' equity of $302.1 million. In comparison, we had cash, cash equivalents and short-term investments of $491.0 million and stockholders' equity of $147.4 million as of December 31, 2008. Our cash, cash equivalents and short-term investments at December 31, 2009 included $30.7 million, which is Regulus' cash, cash equivalents and short-term investments that will not be included in our cash balance beginning in 2010 as a result of the accounting change for Regulus. See Note 1, *Organization and Significant Accounting Policies*, for a more detailed explanation of this change. At December 31, 2009, we had consolidated working capital of $484.7 million, compared to $393.7 million at December 31, 2008. Our cash, cash equivalents and short-term investments, stockholders' equity and consolidated working capital increased primarily as a result of the $175 million we received from AMI in the first quarter of 2009. During 2009, we also received more than $35 million in cash from our corporate partnerships.

As of December 31, 2009, our debt and other obligations totaled $140.8 million, compared to $130.0 million at December 31, 2008. The increase in our debt and other obligations was primarily due to the $6.4 million additional draw downs on our equipment financing arrangement and $7.1 million of non-cash amortization of the debt discount recorded in 2009 as a result of adopting the accounting standard related to our 2⁵⁄₈ percent convertible notes offset, in part, by the $2.8 million of principal payments we made against our equipment financing arrangement. The new accounting standard did not impact our cash, cash equivalents and short-term investments but decreased the carrying value of our $162.5 million convertible notes to $125.1 million and $118.0 million at December 31, 2009 and 2008, respectively, with corresponding increases to stockholders' equity. For additional information, see Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of December 31, 2009. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2⁵⁄₈ percent Convertible Subordinated Notes	$ 237.1	$ 4.3	$ 8.6	$ 171.0	$ 53.2

(principal and interest payable)					
GSK Convertible Promissory Note (principal and accrued interest)	$ 5.3	$ —	$ 5.3	$ —	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 10.8	$ 4.8	$ 6.0	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.6	$ 0.1	$ 0.1	$ 0.1	$ 1.3
Operating Leases	$ 16.9	$ 3.3	$ 4.5	$ 2.4	$ 6.7
Total	$ 271.7	$ 12.5	$ 24.5	$ 173.5	$ 61.2

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a convertible promissory note Regulus issued to GSK, equipment financing arrangements and other obligations.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2⅝ percent, which is payable semi-annually. The 2⅝ percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the 2⅝ percent notes may also require us to repurchase the 2⅝ percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the 2⅝ percent notes being repurchased plus unpaid interest. Using the net proceeds from the issuance of our 2⅝ percent notes, in 2007, we repaid the entire $125 million of our 5½ percent convertible subordinated notes due 2009.

In connection with the strategic alliance with GSK in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25 percent at December 31, 2009. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. In February 2010, Regulus formed a new alliance with GSK and issued a second $5 million convertible promissory note, guaranteed by us and Alnylam, that will convert into Regulus common stock in the future under certain specified circumstances. For additional information, see Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. We have drawn down $13.0 million in principal under this loan agreement at a weighted average interest rate of 6.65 percent. The carrying balance under this loan agreement at December 31, 2009 and 2008 was $10.0 million and $6.5 million, respectively.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2009 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 be required to incur additional cash expenditures related to our obligations under any new agreement we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like securing lines of credit, refinancing our existing debt, issuing debt instruments, or issuing additional shares of our common stock. 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 invest our excess cash in highly liquid short-term investments that we typically hold 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 2009 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

Based on our evaluation as of the end of the period covered by this report on Form 10-K, our principal executive officer and principal financial officer have concluded that our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) were effective as of December 31, 2009 to ensure that information required to be disclosed in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms.

Changes in Internal Control over Financial Reporting

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

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2009, management, with the participation of the chief executive officer and chief financial officer, assessed the effectiveness of Isis' internal control over financial reporting based on the criteria for effective internal control over financial reporting established in "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission. Based on the assessment, management determined that Isis maintained effective internal control over financial reporting as of December 31, 2009.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2009, as stated in their attestation report, which is included elsewhere herein.

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, 2009, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Isis Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

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

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

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

In our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2009, 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, 2009 and 2008, and the related statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2009 of Isis Pharmaceuticals, Inc. and our report dated March 1, 2010 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2010

Item 9B. Other Information

In September 2007, we entered into a collaboration with OMJP to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs. The collaboration ended. In February 2010 we regained the rights to drugs from both the glucagon receptor and glucocorticoid receptor programs. We intend to move a more potent inhibitor for our GCGR program forward that was identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "Election of Directors," "Nominating, Governance and Review Committee" and "Audit Committee," respectively, contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 16, 2010 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2010 Annual Meeting of Stockholders to be held on June 2, 2010.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics" contained in the Proxy Statement. We have filed our Code of Ethics as an exhibit to this Report on Form 10-K.

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

Item 11. Executive Compensation

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

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

We incorporate by reference the information required by this item to the information under the captions "Security Ownership of Certain Beneficial Owners and Management" contained in the Proxy Statement.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2009.

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)	5,586,426	$ 10.43	3,371,058(c)
Equity compensation plans not approved by stockholders(b)	3,046,910	$ 13.62	5,566
Total	8,633,336	$ 11.56	3,376,624

(a) Consists of three Isis plans: 1989 Stock Option Plan, 2002 Non-Employee Directors' Stock Option Plan and ESPP.

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

(c) Of these shares, 98,769 remained available for purchase under the ESPP as of December 31, 2009. 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, 2009, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 3,046,910 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 2,937,524 shares had been exercised under the 2000 Plan, and 5,566 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. Options granted pursuant to the April 2003 stock option exchange program as discussed in the Notes to the Consolidated Financial Statements, expired on December 31, 2008. 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 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and 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 will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

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

In the event of:

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

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

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

We incorporate by reference the information required by this item to the information under the caption "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accountant Fees and Services

We incorporate by reference the information required by this item to the information under the caption "Ratification of Selection of Independent Auditors" contained in the Proxy Statement.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 68.

(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 1st day of March, 2010.

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 B. Lynne Parshall, 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)	March 1, 2010
/s/ B. LYNNE PARSHALL Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 1, 2010
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 1, 2010
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	March 1, 2010
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	March 1, 2010
/s/ FREDERICK T. MUTO Frederick T. Muto	Director	March 1, 2010
/s/ JOHN C. REED, M.D. PH.D. John C. Reed, M.D., Ph.D.	Director	March 1, 2010
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 1, 2010

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(3)
3.3	Amended and Restated Bylaws.(18)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.2	Specimen Common Stock Certificate.(1)
4.3	Form of Right Certificate.(17)
4.4	Stock Purchase Agreement between the Registrant and Genzyme Corporation dated January 7, 2008. (8)
4.5	Indenture, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of $2^{5}/_{8}$ percent Convertible Subordinated Note due 2027.(14)

4.6	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein.(14)
4.7	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted).(3)
4.8	Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC.(3)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2*	Registrant's 1989 Stock Option Plan, as amended.(2)
10.3*	Registrant's Amended and Restated Employee Stock Purchase Plan.(20)
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.(10)
10.6	Drug Development and License Option Agreement dated December 2, 2009 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).
10.7	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.8	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.9	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.10	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008 (with certain confidential information deleted). (12)
10.11	Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007 (with certain confidential information deleted).(30)
10.12	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics

	Ltd dated February 8, 2008 (with certain confidential information deleted).(8)
10.13	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009 (with certain confidential information deleted).
10.14	VLA4 Partner Support Agreement between the Registrant and Teva Pharmaceutical Industries Ltd dated February 8, 2008 (with certain confidential information deleted).(8)
10.15	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. (with certain confidential information deleted) (22)
10.16	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.17	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.18	Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(23)
10.19*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan.(13)
10.20*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(29)
10.21	Product Development and Commercialization Agreement between Regulus Therapeutics LLC and Glaxo Group Limited dated April 17, 2008 (with certain confidential information deleted). (12)
10.22*	Amended and Restated Severance Agreement dated December 3, 2008 between Isis and Stanley T. Crooke. (21)
10.23*	Amended and Restated Severance Agreement dated December 3, 2008 between Isis and B. Lynne Parshall. (21)
10.24	Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(28)
10.25	Amendment No. 1 to Sale Agreement dated October 14, 2007 between Isis and Drug Royalty Trust 3.(15)
10.26	Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc. (31)

10.27	Amendment No. 1 to License Agreement between the Registrant and Eyetech.(16)
10.28	Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(16)
10.29	Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(16)
10.30*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(16)
10.31*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(16)
10.32*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(16)
10.33*	Employment Agreement dated December 29. 2008 between Regulus Therapeutics and Kleanthis G. Xanthopoulos, PhD (31)
10.34	Amendment No.1 to Rights Agreement dated April 7, 2005.(27)
10.35	First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009

10.36	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(23)
10.37	Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(23)
10.38	Pre-Clinical Development Collaboration Agreement dated March 23, 2007 between the Registrant and Korean Institute of Toxicology (with certain confidential information deleted). (31)
10.39	Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. (with certain confidential information deleted).(31)
10.40	Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(14)
10.41	Collaboration and License Agreement between the Registrant and Bristol-Myers Squibb Company dated May 8, 2007 (with certain confidential information deleted). (7)
10.42	Research Agreement dated October 22, 2007 between the Registrant and CHDI, Inc. (with certain confidential information deleted).(4)
10.43	Founding Investor Rights Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated January 1, 2009 (with certain confidential information deleted).(6)
10.44	Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated January 1, 2009 (with certain confidential information deleted).(6)
10.45	Amendment No. 1 to Amended and Restated License Agreement between the Registrant and Oncogenex Technologies Inc. dated December 18, 2009.
14.1	Registrant's Code of Ethics and Business Conduct.(21)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney.(32)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)

(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 Current Report on Form 8-K, filed with the SEC on April 15, 2009 and incorporated herein by reference.

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

(4) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2007 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, 2007 and incorporated herein by reference.

(6) 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.

(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2007 and incorporated herein by reference.

(8) 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.

(9) 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.

(10) 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.

(11) 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.

(12) 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.

(13) Filed as an exhibit to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.

(14) Filed as an exhibit to Registrant's Current Report on Form 8-K dated January 24, 2007 and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Current Report on Form 8-K dated October 17, 2007 and incorporated herein by reference.

(16) 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.

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

(18) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed June 4, 2009 and incorporated herein by reference.

(19) 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.

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

(21) Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 4, 2008 and incorporated herein by reference.

(22) 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.

(23) 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.

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

(25) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 7, 2002 and incorporated herein by reference.

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

(27) Filed as an exhibit to Registrant's Current Report on Form 8-K dated April 7, 2005 and incorporated herein by reference.

(28) 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.

(29) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2001 and incorporated herein by reference.

(30) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2007 and incorporated herein by reference.

(31) 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.

(32) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2009, reference is made to page 65.

* 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, 2009 and 2008, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2009. 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, 2009 and 2008, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2009, in conformity with U.S. generally accepted accounting principles.

As discussed in Note 1 to the consolidated financial statements, the Company adopted Financial Accounting Standards Board Statement No. 160, *Noncontrolling Interests in Consolidated Financial statements* (SFAS 160) (codified in FASB ASC Topic 810, *Consolidations*) effective as of January 1, 2009 and retroactively adjusted all periods presented in the consolidated financial statements for this change.

As discussed in Note 4 to the consolidated financial statements, the Company adopted Financial Accounting Standards Board Staff Position No. APB 14-1, *Accounting for Convertible Debt Instruments That May Be Settled in Cash Upon Conversion (Including Partial Cash Settlement)* (FSP APB 14-1) (codified in FASB ASC Topic 470, *Debt with Conversions and Other Options*) effective as of January 1, 2009 and retroactively adjusted all periods presented in the consolidated financial statements for this change.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the effectiveness of Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2009, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 1, 2010 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2010

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

	December 31, 2009	December 31, 2008
ASSETS		
Current assets:		
Cash and cash equivalents	$ 105,255	$ 217,918
Short-term investments	469,057	273,080
Contracts receivable	10,899	4,121
Inventories	2,768	2,718
Other current assets	8,147	5,085
Assets from discontinued operations (including cash and cash equivalents of $6.1 million as of December 31, 2008)	—	15,462

Total current assets	596,126	518,384
Property, plant and equipment, net	27,338	17,371
Licenses, net	14,542	16,861
Patents, net	15,909	16,260
Deposits and other assets	3,269	3,900
Total assets	$ 657,184	$ 572,776
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,696	$ 5,710
Accrued compensation	7,135	6,835
Income taxes payable	7,323	—
Accrued liabilities	12,339	9,557
Current portion of long-term obligations	4,270	2,065
Current portion of deferred contract revenue	75,681	92,662
Liabilities from discontinued operations	—	7,870
Total current liabilities	111,444	124,699
$2^5/_8$ percent convertible subordinated notes	125,100	117,993
Long-term obligations, less current portion	11,478	9,938
Long-term deferred contract revenue	107,097	172,766
Total liabilities	355,119	425,396
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 98,850,934 and 97,172,380 shares issued and outstanding at December 31, 2009 and 2008, respectively	99	97
Additional paid-in capital	985,620	960,361
Accumulated other comprehensive income	2,153	982
Accumulated deficit	(696,150)	(851,216)
Total Isis Pharmaceuticals, Inc. stockholders' equity	291,722	110,224
Noncontrolling interest in Regulus Therapeutics Inc.	10,343	4,737
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	—	32,419
Total stockholders' equity	302,065	147,380
Total liabilities and stockholders' equity	$ 657,184	$ 572,776

See accompanying notes.

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

	Years Ended December 31,		
	2009	2008	2007
Revenue:			
Research and development revenue under collaborative agreements	$ 108,131	$ 98,853	$ 22,319
Licensing and royalty revenue	13,469	8,337	36,025
Total revenue	121,600	107,190	58,344
Expenses:			
Research and development	134,623	106,439	78,204
General and administrative	14,515	13,811	13,059
Total operating expenses	149,138	120,250	91,263
Loss from operations	(27,538)	(13,060)	(32,919)
Other income (expense):			
Investment income	6,361	11,318	11,443
Interest expense	(12,672)	(11,812)	(12,872)
Gain (loss) on investments, net	2,084	(965)	3,510
Loss on early retirement of debt	—	—	(3,212)
Loss from continuing operations, before income tax expense	(31,765)	(14,519)	(34,050)
Income tax expense	(3,191)	—	—
Net loss from continuing operations, including income tax expense	(34,956)	(14,519)	(34,050)
Discontinued operations:			

Loss from discontinued operations	(29)	(8,387)	(6,029)
Gain on sale of Ibis Biosciences, Inc., net of tax	185,657	—	—
Net income (loss) from discontinued operations, net of tax	185,628	(8,387)	(6,029)
Net income (loss)	150,672	(22,906)	(40,079)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	4,394	4,734	629
Net loss attributable to noncontrolling interest in Symphony GenIsis, Inc.	—	—	23,157
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc	—	—	(125,311)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 155,066	$ (18,172)	$ (141,604)
Basic and diluted net income (loss) per share:			
Net loss from continuing operations	$ (0.31)	$ (0.10)	$ (0.12)
Net income (loss) from discontinued operations	1.89	(0.09)	(0.07)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc	—	—	(1.50)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1.58	$ (0.19)	$ (1.69)
Shares used in computing basic and diluted net income (loss) per share	98,109	94,566	83,739

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2009, 2008 and 2007
(In thousands)

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests			
	Common stock		Additional paid in	Accumulated other comprehensive	Accumulated				Total stockholders'
Description	Shares	Amount	capital	income	deficit	Regulus	Ibis	Symphony GenIsis	equity
Balance at December 31, 2006	82,284	$ 82	$ 880,954	$ 4,278	$ (816,751)	$ —	$ —	$ 29,339	$ 97,902
Retroactive adoption of accounting standard	—	—	54,641	—	—	—	—	—	54,641
Comprehensive loss:									
Net loss	—	—	—	—	(16,293)	(629)	—	(23,157)	(40,079)
Change in unrealized losses	—	—	—	(3,740)	—	—	—	—	(3,740)
Comprehensive loss	—	—	—	—	—	—	—	—	(43,819)
Options exercised and employee stock purchase plan issuances	1,510	2	11,349	—	—	—	—	—	11,351
Warrants exercised	61	—	—	—	—	—	—	—	—
Share-based compensation expense	—	—	9,910	—	—	—	—	—	9,910
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	10,000	—	—	10,000
Acquisition of Symphony GenIsis, Inc.	—	—	(125,311)	—	—	—	—	(6,182)	(131,493)
Issuance of common stock for Symphony GenIsis acquisition	3,384	3	51,090	—	—	—	—	—	51,093
Balance at December 31, 2007	87,239	$ 87	$ 882,633	$ 538	$ (833,044)	$ 9,371	$ —	$ —	$ 59,585
Comprehensive loss:									
Net loss	—	—	—	—	(18,172)	(4,734)	—	—	(22,906)
Change in unrealized gains	—	—	—	444	—	—	—	—	444
Comprehensive loss	—	—	—	—	—	—	—	—	(22,462)
Options exercised and employee stock purchase plan issuances	1,510	2	12,549	—	—	—	—	—	12,551
Warrants exercised	3,423	3	160	—	—	—	—	—	163
Share-based compensation expense	—	—	15,063	—	—	—	—	—	15,063
Issuance of common stock to Genzyme	5,000	5	49,956	—	—	—	—	—	49,961
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	100	—	—	100
AMI's capital contribution to noncontrolling interest	—	—	—	—	—	—	32,419	—	32,419
Balance at December 31, 2008	97,172	$ 97	$ 960,361	$ 982	$ (851,216)	$ 4,737	$ 32,419	$ —	$ 147,380
Balance at December 31, 2008	97,172	$ 97	$ 960,361	$ 982	$ (851,216)	$ 4,737	$ 32,419	$ —	$ 147,380
Comprehensive income:									
Net income (loss)	—	—	—	—	155,066	(4,394)	—	—	150,672
Change in unrealized gains, net of $0.8 million of tax expense	—	—	—	2,819	—	—	—	—	2,819
Reclassification adjustment for realized gains included in net income	—	—	—	(1,648)	—	—	—	—	(1,648)
Comprehensive income	—	—	—	—	—	—	—	—	151,843
Options exercised and employee stock purchase plan issuances	1,670	2	13,154	—	—	—	—	—	13,156
Warrants exercised	9	—	—	—	—	—	—	—	—
Excess tax benefits on share-based compensation	—	—	278	—	—	—	—	—	278
Share-based compensation expense	—	—	11,827	—	—	—	—	—	11,827
Sale of Ibis to AMI	—	—	—	—	—	—	(32,419)	—	(32,419)
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	10,000	—	—	10,000
Balance at December 31, 2009	98,851	$ 99	$ 985,620	$ 2,153	$ (696,150)	$ 10,343	$ —	$ —	$ 302,065

See accompanying notes.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2009	2008	2007
Operating activities:			
Net income (loss)	$ 150,672	$ (22,906)	$ (40,079)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Depreciation	3,935	2,868	2,667
Amortization of patents	3,024	1,610	1,623
Amortization of licenses	2,344	2,339	2,335
Amortization of premium (discount) on investments, net	2,026	(225)	(773)
Amortization of debt issuance costs	507	529	644
Amortization of 2 5/8 percent convertible subordinated notes discount	7,107	6,477	5,568
Share-based compensation expense	13,385	15,063	9,910
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	—	(2,103)	—
Gain from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	(185,657)	—	—
Gain from derivative instruments issued to Abbott Molecular Inc.	—	(5,326)	—
(Gain) loss on investments, net	(2,084)	965	(3,510)
Loss on early retirement of debt	—	—	3,212
Non-cash losses related to patents and property, plant and equipment	696	1,877	896
Excess tax benefits on share-based compensation	(278)	—	—
Changes in operating assets and liabilities:			
Contracts receivable	(6,778)	1,238	(3,782)
Inventories	(17)	(1,323)	(1,956)
Other current and long-term assets	(955)	(2,657)	(494)
Accounts payable	(3,652)	962	(794)
Accrued compensation	(4,371)	(3,255)	4,239
Income taxes payable	(10,013)	—	—
Accrued liabilities	4,318	4,923	723
Deferred contract revenue	(82,650)	210,975	55,665
Net cash (used in) provided by operating activities	(108,441)	212,031	36,094
Investing activities:			
Purchases of short-term investments	(776,381)	(483,129)	(95,371)
Proceeds from the sale of short-term investments	578,886	265,951	119,956
Purchases of property, plant and equipment	(13,414)	(13,665)	(2,293)
Acquisition of licenses and other assets	(2,880)	(3,402)	(2,717)
Purchases of strategic investments	(1,349)	—	—
Proceeds from the sale of strategic investments	2,848	—	5,181
Acquisition of Symphony GenIsis, Inc.	—	—	(80,400)
Net cash used in investing activities	(212,290)	(234,245)	(55,644)
Financing activities:			
Net proceeds from issuance of equity	13,156	12,714	11,351
Excess tax benefits on share-based compensation	278	—	—
Proceeds from issuance of convertible promissory note to GlaxoSmithKline	—	5,000	—
Proceeds from equipment financing arrangement	6,394	7,048	—
Proceeds from issuance of 2 5/8 percent convertible subordinated notes, net of issuance costs	—	—	157,056
Principal and redemption premium payment on prepayment of the 5 1/2 percent convertible subordinated notes	—	—	(127,021)
Principal payments on debt and capital lease obligations	(2,827)	(7,239)	(7,736)
Proceeds from stock purchase by Genzyme Corporation, net of fees	—	49,962	—
Proceeds from sale of Ibis Biosciences, Inc to Abbott Molecular Inc.	175,000	40,000	—
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	10,000	100	10,000
Net cash provided by financing activities	202,001	107,585	43,650
Net (decrease) increase in cash and cash equivalents	(118,730)	85,371	24,100
Cash and cash equivalents at beginning of year	223,985	138,614	114,514
Cash and cash equivalents (including cash and cash equivalents classified as assets from discontinued operations of $0, $6.1 million and $0 at December 31, 2009, 2008 and 2007, respectively) at end of year	$ 105,255	$ 223,985	$ 138,614
Supplemental disclosures of cash flow information:			
Interest paid	$ 4,883	$ 4,607	$ 6,212
Income taxes paid	$ 13,205	$ —	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 870	$ 2,873	$ 1,013
Common stock issued for Symphony GenIsis, Inc. acquisition	$ —	$ —	$ 51,093

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 subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. On September 27, 2007, we purchased all of the equity in Symphony GenIsis as more fully described in Note 7—*Collaborative Arrangements and Licensing Agreements*. In addition to our wholly owned subsidiaries, our consolidated financial statements include one variable interest entity, Regulus Therapeutics Inc., for which we are the primary beneficiary. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we have presented Ibis' financial position and results of operations separately as discontinued operations in our consolidated financial statements. We have reclassified amounts in the prior period financial statements to conform to the current period presentation. Prior to the sale of Ibis and the acquisition of Symphony GenIsis, we identified Ibis and Symphony GenIsis as variable interest entities that we consolidated. We have eliminated all significant intercompany balances and transactions.

The consolidated financial statements have been adjusted for the required retroactive adoption of the accounting standards for convertible debt instruments that may be settled in cash upon conversion and for reclassification of noncontrolling interests. See the Noncontrolling interests section within this Note and Note 4, *Long-Term Obligations and Commitments*, for additional information.

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 income (loss) per share

We compute basic net income (loss) per share by dividing the net income (loss) by the weighted-average number of common shares outstanding during the period. As we incurred a loss from continuing operations for the years ended December 31, 2009, 2008 and 2007, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would be anti-dilutive:

- $5^1/_2$ percent convertible subordinated notes;
- $2^5/_8$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory note;
- Dilutive stock options;
- Warrants issued to Symphony GenIsis Holdings LLC; and
- Warrants issued for the Private Placement Financing

Computations for basic and diluted net income (loss) per share are as follows: (in thousands, except per share amounts)

	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the year ended December 31, 2009			
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (30,562)		
Net income from discontinued operations	185,628		
Total basic and diluted net income	$ 155,066	98,109	$ 1.58
For the year ended December 31, 2008			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,785)		
Net loss from discontinued operations, net of taxes	(8,387)		
Total basic and diluted net loss	$ (18,172)	94,566	$ (0.19)
For the year ended December 31, 2007			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (10,264)		
Net loss from discontinued operations	(6,029)		
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	(125,311)		
Total basic and diluted net loss	$ (141,604)	83,739	$ (1.69)

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and we record contract revenue as we earn it based on the performance requirements of our collaborative research and development contracts. We recognize contract revenue for which no further performance obligations exist when we receive the payments and when we are reasonably certain we can collect the receivable. We record payments received in excess of amounts earned as deferred contract revenue. We expense research and development costs as incurred. For the years ended December 31, 2009, 2008 and

2007, research and development costs of approximately $57.1 million, $45.0 million, and $9.4 million, respectively, were related to collaborative research and development arrangements.

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 under current accounting rules. In those instances where 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

We often enter into collaborations under which we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to estimate our period of performance when the agreements we enter into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. 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. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable, the amounts are not refundable and we have no future performance obligations related to the achievement of the milestone.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate fair value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represented value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan. See further discussion about our collaboration with Genzyme 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.

Concentration of credit risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. We place our cash equivalents and certain of our short-term investments with high credit-quality financial institutions. We invest our excess cash primarily in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury. We and our audit committee establish guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, cash equivalents and short-term investments

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

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our majority owned subsidiary, which we consolidate with our financial results. 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. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. When 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 2009, we recognized a $2.1 million gain on investments consisting of a $2.5 million gain when we sold all of the common stock of OncoGenex Pharmaceuticals Inc. that we owned and a $574,000 gain that we realized on our available-for-sale securities offset by a $1.0 million valuation

allowance we recorded related to our investment in Altair Therapeutics Inc. Because realization of our Altair investment is uncertain we recorded a full valuation allowance. See further discussion about our investment in Altair in Note 7, *Collaborative Arrangements and Licensing Agreements*. During 2008, we recognized a $965,000 loss on investments consisting of a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex and a $198,000 gain that we realized on our available-for-sale securities. See further discussion about our investment in OncoGenex in Note 7, *Collaborative Arrangements and Licensing Agreements*. During 2007, we sold the remainder of our equity securities of Alnylam Pharmaceuticals, Inc. that we owned resulting in a realized gain of $3.5 million. We determined that there were no other-than-temporary declines in value of our investments in 2009 and 2007.

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 allocated 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-off for the years ended December 31, 2009, 2008 and 2007. Total inventory, which consisted of raw materials, was $2.8 million and $2.7 million as of December 31, 2009 and 2008, respectively.

Property, plant and equipment

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

	December 31,	
	2009	2008
Equipment and computer software	$ 37,098	$ 30,328
Leasehold improvements	24,822	17,705
Furniture and fixtures	1,777	1,775
	63,697	49,808
Less accumulated depreciation	(36,359)	(32,437)
	$ 27,338	$ 17,371

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

Equipment	5 years
Manufacturing Equipment	10 years
Computer software and hardware	3 years
Furniture and fixtures	5 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. Our license from Idera Pharmaceuticals, Inc., comprised the majority of the license balance as of December 31, 2009 and 2008. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately 8 years and 15 years. The cost of our licenses at December 31, 2009 and 2008 was $36.1 million and $36.0 million, respectively. Accumulated amortization related to licenses was $21.6 million and $19.1 million at December 31, 2009 and 2008, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2010 and 2011 and $2.2 million for the years ending December 31, 2012, 2013 and 2014.

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patent. The weighted average remaining amortizable life of issued patents was 2.9 years and 3.4 years at December 31, 2009 and 2008, respectively. In 2009, 2008 and 2007, we recorded a non-cash charge of $696,000, $1.8 million and $887,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values except in 2008 when the charge primarily related to the assignment of patents to certain of our partners.

Accumulated amortization related to patents was $15.5 million and $11.8 million at December 31, 2009 and 2008, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)

2010	$	1.8
2011	$	1.4
2012	$	1.1
2013	$	0.8
2014	$	0.6

Fair value of financial instruments

We have determined the estimated 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 of comparable instruments.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. We recorded a charge of $696,000, $1.9 million and $887,000 for the years ended December 31, 2009, 2008 and 2007, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values except in 2008 when the charge primarily related to the assignment of patents to certain of our partners.

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. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

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. For 2009, our consolidated financial statements included one variable interest entity, Regulus, for which we were the primary beneficiary. Prior to the sale of Ibis to AMI in January 2009 and the acquisition of Symphony GenIsis in September 2007, we identified Ibis and Symphony GenIsis as variable interest entities that we consolidated.

Stock-based compensation

We estimate the fair value of stock-based payment awards on the date of grant using an option-pricing model. We recognize the value of the portion of the award that we ultimately expect to vest as expense over the requisite service period as stock-based compensation expense in our Consolidated Statements of Operations. We recognize compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We utilize the Black-Scholes model as our method of valuation for stock-based awards granted. On the grant date, we use our stock price as well as 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 account for stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, by estimating their fair value. Until the stock option is vested, we remeasure the fair value at each reporting period. We recognize the expense over the period of time we require the non-employee to perform services.

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

Comprehensive income (loss)

We are required to display comprehensive income (loss) and its components as part of our full set of consolidated financial statements. The measurement and presentation of net income (loss) did not change. Comprehensive income (loss) is comprised of net income (loss) and certain changes in stockholders' equity that are excluded from net income (loss). We are required to include unrealized holding gains and losses, net of taxes, and reclassification adjustment for realized gains and losses on our available-for-sale securities, which we report separately in stockholders' equity, in accumulated other comprehensive income (loss). We include comprehensive income (loss) for the years ended December 31, 2009, 2008 and 2007 in our Consolidated Statements of Stockholders' Equity.

Noncontrolling Interests

On January 1, 2009, we adopted an accounting standard, which recharacterizes the accounting and reporting for minority interests as noncontrolling interests and classifies them as a component of stockholders' equity. Although the adoption of this accounting standard did not impact our results of operations and financial position, it required us to reclassify noncontrolling interests as stockholders' equity, include the net loss attributable to noncontrolling interests as part of our consolidated net income (loss) and provide additional disclosures as part of our consolidated financial statements. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our consolidated financial statements.

Convertible debt

On January 1, 2009, we adopted an accounting standard, which requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$ percent convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the expected life of the debt as additional non-cash interest expense. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our consolidated financial statements. For additional information, see Note 4, *Long-Term Obligations and Commitments*.

Segment information

We operate in two separate segments; Drug Discovery and Development and Regulus. We provide segment financial information and results for our Drug Discovery and Development segment and our Regulus subsidiary based on the segregation of revenues and expenses we use for management's assessment of operating performance and operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment. Prior to completing the sale of Ibis to AMI, we reported Ibis as a separate segment. As a result of the sale, we have presented the operating results of Ibis separately as discontinued operations for all periods presented in our 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, which includes our money market funds and treasury securities classified as available-for-sale securities and 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 an entity to develop its own assumptions.

Below is a table of our assets that we measure at fair value on a recurring basis. For the following major security types, we break down the inputs used to measure fair value at December 31, 2009 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 87,959	$ 87,959	$ —	$ —
Corporate debt securities (2)	144,285	—	144,285	—
Debt securities issued by U.S. government agencies (2)	261,329	—	261,329	—
Debt securities issued by the U.S. Treasury (2)	63,168	63,168	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	275	—	275	—
Equity securities (3)	3,874	3,874	—	—
Total	$ 560,890	$ 155,001	$ 405,889	$ —

(1) Included in cash and cash equivalents on our Consolidated Balance Sheet.

(2) Included in short-term investments on our Consolidated Balance Sheet.

(3) Included in other current assets on our Consolidated Balance Sheet.

Income Taxes

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

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

Impact of recently issued accounting standards

In June 2009, the Financial Accounting Standards Board issued a new accounting standard to replace the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impact the variable interest entity's economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. When we

adopt this new standard in the first quarter of 2010, we will prospectively change the way we account for our variable interest in Regulus. Since we and Alnylam share the ability to impact Regulus' economic performance, we will no longer be the primary beneficiary of Regulus. As a result, beginning in the first quarter of 2010, we will deconsolidate Regulus from our consolidated financial statements and will begin to account for our ownership interest in Regulus using the equity method of accounting. This means that we will no longer include Regulus' revenue and operating expenses in our operating results. Instead we will include our share of Regulus' operating results on a separate line in the other income section of our Statement of Operations called "Equity in loss of Regulus Therapeutics Inc." On the balance sheet, we will present our share of Regulus' net assets on a separate line in the non-current assets section called "Investment in Regulus Therapeutics Inc.," and therefore we will no longer include Regulus' cash in our cash balance.

2. Discontinued Operations

In 2008, AMI purchased approximately 18.6 percent of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement (the "Stock Purchase Agreement"). Under the Stock Purchase Agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. See Note 7—*Collaborative Arrangements and Licensing Agreements* for additional information about our strategic alliance with AMI.

Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation on our consolidated financial statements. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations for the year ended December 31, 2009 primarily consisted of the $202.5 million gain related to the sale of Ibis to AMI less $16.8 million of income tax expense. The components of discontinued operations for the periods presented are as follows (in thousands):

	Year Ended December 31,		
	2009	2008	2007
Revenue	$ —	$ 12,586	$ 11,277
Total operating expenses	35	28,393	17,306
Loss from operations	(35)	(15,807)	(6,029)
Other income, net	—	5,317	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6	2,103	—
Loss from discontinued operations	(29)	(8,387)	(6,029)
Gain on sale of Ibis Biosciences, Inc., net of tax	185,657	—	—
Net income (loss) from discontinued operations, net of tax	$ 185,628	$ (8,387)	$ (6,029)

At December 31, 2008, we had the following assets and liabilities classified as assets and liabilities from discontinued operations in our accompanying Consolidated Balance Sheets (in thousands):

Cash and cash equivalents	$ 6,067
Contracts receivable	818
Inventories	1,422
Property, plant and equipment, net	2,792
Patents, net	2,001
Other assets	2,362
Assets from discontinued operations	$ 15,462
Accounts payable	2,632
Accrued compensation	371
Accrued liabilities	1,982
Notes payable	585
Deferred contract revenue	2,300
Liabilities from discontinued operations	$ 7,870
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	$ 32,419

We have not separately classified cash flows from discontinued operations in our Consolidated Statement of Cash Flows.

3. Investments

As of December 31, 2009, our excess cash was primarily invested in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury. 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, 2009:

One year or less	61%
After one year but within five years	39%
Total	100%

At December 31, 2009, we had an ownership interest of less than 20 percent in each of five private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S, Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair and Excaliard Pharmaceuticals, Inc., which are privately-held and Antisense Therapeutics

Limited and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting. During 2009, we sold all of the common stock of OncoGenex that we owned resulting in a realized gain of $2.5 million. See further discussion about our investment in OncoGenex in Note 7—*Collaborative Arrangements and Licensing Agreements*.

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

December 31, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 102,598	$ 174	$ (34)	$ 102,738
Debt securities issued by U.S. government agencies	151,008	178	(17)	151,169
Debt securities issued by the U.S. Treasury	32,027	42	(10)	32,059
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	275
Total securities with a maturity of one year or less	285,908	394	(61)	286,241
Corporate debt securities	41,388	262	(103)	41,547
Debt securities issued by U.S. government agencies	110,313	65	(218)	110,160
Debt securities issued by U.S. Treasury	31,136	2	(29)	31,109
Total securities with a maturity of more than one year	182,837	329	(350)	182,816
Subtotal	$ 468,745	$ 723	$ (411)	$ 469,057
Equity securities:				
Current portion (included in Other current assets)	$ 1,229	$ 2,645	$ —	$ 3,874
Long-term portion (included in Deposits and other assets)	625	—	—	625
Subtotal	$ 1,854	$ 2,645	$ —	$ 4,499
	$ 470,599	$ 3,368	$ (411)	$ 473,556

December 31, 2008	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 111,569	$ 150	$ (307)	$ —	$ 111,412
Debt securities issued by U.S. government agencies	111,112	838	(19)	—	111,931
Debt securities issued by the U.S. Treasury	12,939	44	—	—	12,983
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	—	275
Total securities with a maturity of one year or less	235,895	1,032	(326)	—	236,601
Corporate debt securities	13,608	5	(371)	—	13,242
Debt securities issued by U.S. government agencies	23,199	56	(18)	—	23,237
Total securities with a maturity of more than one year	36,807	61	(389)	—	36,479
Subtotal	$ 272,702	$ 1,093	$ (715)	$ —	$ 273,080
Equity securities:					
Current portion (included in Other current assets)	$ 2,380	$ 604	$ —	$ (1,163)	$ 1,821
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 3,005	$ 604	$ —	$ (1,163)	$ 2,446
	$ 275,707	$ 1,697	$ (715)	$ (1,163)	$ 275,526

Investments we consider to be temporarily impaired at December 31, 2009 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses	More than 12 months of temporary impairment: Estimated Fair Value	More than 12 months of temporary impairment: Unrealized Losses	Total temporary impairment: Estimated Fair Value	Total temporary impairment: Unrealized Losses
Corporate debt securities	56	$ 49,355	$ (133)	$ 1,657	$ (4)	$ 51,012	$ (137)
Debt securities issued by U.S. government agencies	26	86,121	(235)	—	—	86,121	(235)
Debt securities issued by the U.S. Treasury	6	37,045	(39)	—	—	37,045	(39)
Total temporarily impaired securities	88	$ 172,521	$ (407)	$ 1,657	$ (4)	$ 174,178	$ (411)

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

4. Long-Term Obligations and Commitments

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

	December 31,

	2009	2008
GlaxoSmithKline convertible promissory note, including accrued interest	$ 5,342	$ 5,179
2 5/8 percent convertible subordinated notes	125,100	117,993
Equipment financing arrangement	10,046	6,463
Other obligations	360	361
Total	$ 140,848	$ 129,996
Less: current portion	(4,270)	(2,065)
Total Long-Term Obligations	$ 136,578	$ 127,931

GlaxoSmithKline Convertible Promissory Note

In connection with the strategic alliance with GlaxoSmithKline, or GSK, in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25 percent at December 31, 2009. At December 31, 2009, the principal and accrued interest on the note was $5 million and $342,000, respectively. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. We did not include the effect of the conversion of the note into our common stock in the computation of diluted net income (loss) from continuing operations per share because the effect would have been anti-dilutive.

Convertible Subordinated Notes

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2 5/8 percent, which is payable semi-annually. The 2 5/8 percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. At December 31, 2009, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value was $165.8 million. At December 31, 2008, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value was $162.3 million. We did not include the effect of the conversion of the note into our common stock in the computation of diluted net income (loss) from continuing operations per share because the effect would have been anti-dilutive.

We will be able to redeem the 2 5/8 percent notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the 2 5/8 percent notes may also require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the 2 5/8 percent notes being repurchased plus unpaid interest.

In 2007, we used the net proceeds from the issuance of the 2 5/8 percent notes to repurchase our 5 1/2 percent convertible subordinated notes due in 2009 for a redemption price of $127.0 million plus accrued but unpaid interest. As a result of the repayment of these notes, we recognized a $3.2 million loss on the early extinguishment of debt in 2007, which included a $1.2 million non-cash write-off of unamortized debt issuance costs.

In 2009, we began accounting for the 2 5/8 percent notes using the accounting standard which requires us to assign a value to our convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature that results in us recording our convertible debt at a discount. We amortize the resulting debt discount over the expected life of the debt as additional non-cash interest expense. We retrospectively applied the standard to all periods presented in our consolidated financial statements. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate for the 2 5/8 percent notes was 9.3 percent. As a result, we retrospectively adjusted the carrying value of the 2 5/8 percent notes. Below is a table summarizing the changes to our balance sheet as of December 31, 2008 as a result of adopting this accounting standard (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Debt issuance costs (included in deposits and other assets)	$ 3,943	$ 2,569	$ (1,374)
2 5/8 percent convertible subordinated notes	$ 162,500	$ 117,993	$ (44,507)
Additional paid-in capital	$ 905,721	$ 960,361	$ 54,640
Accumulated deficit	$ (839,708)	$ (851,216)	$ (11,508)

Additionally, we adjusted interest expense for the years ended December 31, 2008 and 2007 to reflect our nonconvertible debt borrowing rate as follows (in thousands):

	As Originally Reported	As Adjusted	Effect of Change	Effect of Change per share (Basic and Diluted)
Interest expense:				
Year ended December 31, 2008	$ 5,603	$ 11,812	$ 6,209	$ 0.07
Year ended December 31, 2007	$ 7,573	$ 12,872	$ 5,299	$ 0.06

As a result of adopting the standard, interest expense for the year ended December 31, 2009 included $6.8 million, or $0.07 for basic and diluted per share, of non-cash interest expense related to the amortization of the debt discount.

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. We have drawn down $13.0 million in principal under this loan agreement at a weighted average interest rate of 6.65 percent. The carrying balance under this loan agreement at December 31, 2009 and 2008 was $10.0 million and $6.5 million, respectively.

Other Obligations

As of December 31, 2009 and 2008, we had approximately $360,000 and $361,000, respectively, under various contractual obligations.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2009 are as follows (in thousands):

2010	$ 9,125
2011	14,262
2012	5,777
2013	4,325
2014	166,826
Thereafter	54,495
Total	$ 254,810

We lease certain office equipment and office and lab space under non-cancelable operating leases with terms through September 2020. The leases on the three buildings we primarily use for laboratory and office space for our drug development business terminate in December 2011. In connection with the sale of our 28,704 square foot manufacturing facility in 2005, we leased back the facility for an initial term of fifteen years with an initial rent of $2.60 per rentable square foot. Under the terms of the lease, the monthly rent will increase five percent every two years. The lease expires in 2020 and provides us an option to extend the lease for up to two five-year periods. In connection with the lease, we executed a stand by letter of credit for $500,000.

Annual future minimum payments under operating leases as of December 31, 2009 are as follows (in thousands):

	Operating Leases
2010	$ 3,309
2011	3,298
2012	1,196
2013	1,207
2014	1,166
Thereafter	6,720
Total minimum payments	$ 16,896

Rent expense for the years ended December 31, 2009, 2008, and 2007 was $4.6 million, $3.8 million, and $3.4 million, respectively. In connection with the sale leaseback of our manufacturing facility, we recognize rent expense on a straight line basis over the lease term resulting in a deferred rent balance of $572,000 and $469,000 at December 31, 2009 and 2008, respectively, which we include in liabilities on our balance sheet.

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, 2009 and 2008, there were no shares of Isis' Series A Convertible Exchangeable 5 percent Preferred Stock or Series B Convertible Exchangeable 5 percent Preferred Stock outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series C Junior Participating Preferred Stock

In December 2000, we adopted a Preferred Share Purchase Rights Plan ("Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right ("Right") for each outstanding share of our common stock, par value $0.001 per share ("Common Shares"), held of record at the close of business on January 10, 2001, and on each subsequently issued share of our common stock. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20 percent or more of our common stock, the Rights permit the holders (except the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a Common Share. Certain conditions allow our Board of Directors to redeem the Rights in whole, but not in part, at a price of $0.001 per Right. As of December 31, 2009 and 2008, there were no shares of the Preferred Shares outstanding.

Common Stock

At December 31, 2009 and 2008, we had 200,000,000 shares of common stock authorized, of which 98,850,934 and 97,172,380 were issued and outstanding, respectively. As of December 31, 2009, total common shares reserved for future issuance were approximately 20,197,719.

We issued 1.7 million and 1.5 million shares of common stock for stock option exercises and the Employee Stock Purchase Plan ("ESPP") purchases for the years ending December 31, 2009 and 2008, respectively. We received net proceeds from these transactions of $13.2 million and $12.6 million in 2009 and 2008, respectively.

In January 2008, Genzyme purchased 5.0 million shares of our common stock for $150.0 million as part of the companies' strategic alliance to develop and commercialize mipomersen. The price Genzyme paid for our common stock represented a significant premium over the fair value of our common stock. Using the Black-Scholes model, we determined that the value of the common stock was $50 million.

Stock Option Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 16,700,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At December 31, 2009, a total of 4,976,426 options were outstanding, options to purchase 3,126,680 shares were exercisable, and 3,145,289 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, provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expired on December 31, 2008. At December 31, 2009, a total of 3,046,910 options were outstanding, 1,468,043 shares were exercisable, and 5,566 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.

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 to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"). In May 2006, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance under the 2002 Plan from 600,000 shares to 850,000 shares. Options under this plan expire 10 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, 2009, a total of 610,000 options were outstanding, 396,250 of the shares issued were exercisable and 127,000 shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the 2000 ESPP and we reserved 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 1.8 million shares authorized in the plan as of December 31, 2009. 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 6 months from the date of purchase beginning with the offering ending in January 1, 2010. During 2009, employees purchased and we issued to employees 116,803 shares under the ESPP at prices ranging from $11.65 to $12.30 per share. At December 31, 2009, 98,769 shares were available for purchase under the ESPP.

Regulus' 2009 Equity Incentive Plan

In February 2009, Regulus' Board of Directors adopted and approved the 2009 Equity Incentive Plan (the "2009 Plan"), which provides for the issuance of non-qualified and incentive stock options for the purchase of up to 5,100,000 shares of common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board. Options expire ten years from the date of grant and vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. At December 31, 2009, a total of 4,847,000 options were outstanding, 2,850,000 shares were exercisable, and 253,000 shares were available for future grant under the 2009 Plan.

In December 2009, Regulus' Board of Directors adopted and amended the 2009 Plan to increase the total number of shares reserved for issuance under the 2009 Plan from 5,100,000 shares to 5,900,000 shares effective January 1, 2010.

Stock Option Activity and Stock-Based Compensation Expense

The following table summarizes Isis' stock option activity for the year ended December 31, 2009 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2008	9,316	$ 10.49		
Granted	1,974	$ 14.52		
Exercised	(1,574)	$ 7.55		
Cancelled/forfeited/expired	(1,083)	$ 13.61		
Outstanding at December 31, 2009	8,633	$ 11.56	4.43	$ 13,566
Exercisable at December 31, 2009	4,991	$ 9.69	3.53	$ 13,013

The following table summarizes information concerning outstanding and exercisable options as of December 31, 2009 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Term	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$3.24–$5.25	950	3.17	$ 5.08	930	$ 5.08
$5.35–$6.81	1,058	3.29	$ 6.19	1,034	$ 6.20
$6.84–$9.77	924	2.99	$ 8.41	813	$ 8.35
$9.85–$11.00	203	3.59	$ 10.41	131	$ 10.48
$11.02–$11.12	1,080	3.94	$ 11.12	778	$ 11.12
$11.13–$14.43	799	5.71	$ 13.34	225	$ 12.62
$14.47–$14.47	1,284	6.00	$ 14.47	0	$ 0
$14.49–$15.32	199	5.97	$ 15.01	29	$ 14.83
$15.38–$15.38	1,340	4.96	$ 15.38	646	$ 15.38
$15.39–$22.83	796	4.94	$ 17.15	405	$ 17.80
	8,633	4.43	$ 11.56	4,991	$ 9.69

The weighted-average estimated fair values of options granted were $7.27, $7.44 and $6.19 for the years ended December 31, 2009, 2008 and 2007, respectively. The total intrinsic value of options exercised during the years ended December 31, 2009, 2008 and 2007 were $9.2 million, $11.2 million and $9.5 million, respectively, which we determined as of the date of exercise. The amounts of cash received from the exercise of stock options were $11.9 million, $11.1 million and $10.3 million for the years ended December 31, 2009, 2008 and 2007, respectively. For the year ended December 31, 2009, the weighted-average fair value of options exercised was $13.39. As of December 31, 2009, total unrecognized compensation cost related to non-vested stock-based compensation plans was $11.0 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.

Stock-based Valuation and Compensation Expense Information

The following table summarizes stock-based compensation expense related to employee and non-employee stock options and the employee stock purchase plan for the year ended December 31, 2009, 2008 and 2007 (in thousands, except per share data), which was allocated as follows:

	Year Ended December 31,		
	2009	2008	2007
Research and development	$ 10,977	$ 10,578	$ 6,745
General and administrative	2,408	2,708	1,553
Non-cash compensation expense related to stock options included in continuing operations	13,385	13,286	8,298
Non-cash compensation expense related to stock options included in discontinued operations	(1,558)	1,777	1,612
Total	$ 11,827	$ 15,063	$ 9,910

Stock-based compensation expense, per share:			
Basic and diluted net loss per share included in continuing operations	$ 0.14	$ 0.14	$ 0.10
Basic and diluted net loss per share included in discontinued operations	(0.02)	0.02	0.02
Total	$ 0.12	$ 0.16	$ 0.12

As part of our Regulus joint venture, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. In addition, we and Alnylam issued our own company's stock options to those employees of each company who were seconded to Regulus under the three companies' limited liability agreement. The seconded employees of Isis became Regulus employees in January 2009 as part of Regulus' conversion to a

C-Corporation. As part of the conversion, both we and Alnylam modified our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. Additionally, in February 2009, Regulus issued options to purchase its own common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board. Regulus records the expenses associated with these options on its books.

Determining Fair Value

Valuation. We utilize the Black-Scholes model as our method of valuation for stock-based awards granted. We recognize the value of the portion of the award that is ultimately expected to vest as expense over the requisite service period as stock-based compensation expense in our Consolidated Statements of Operations. We recognize compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

We estimated the fair value of each stock option grant and the ESPP purchase rights on the date of grant using the Black-Scholes model with the following weighted-average assumptions (annualized percentages), which vary based on type of plan, for the years ended December 31, 2009, 2008 and 2007:

Employee Stock Options:

	December 31,		
	2009	2008	2007
Risk-free interest rate	1.9%	3.1%	4.6%
Dividend yield	0.0%	0.0%	0.0%
Volatility	56.8%	55.2%	63.1%
Expected life	4.9 years	4.6 years	4.6 years

Board of Director Stock Options:

	December 31,		
	2009	2008	2007
Risk-free interest rate	3.4%	3.8%	4.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	61.5%	62.2%	65.5%
Expected life	7.7 years	7.6 years	7.4 years

ESPP:

	December 31,		
	2009	2008	2007
Risk-free interest rate	0.3%	2.8%	5.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	56.5%	61.4%	51.1%
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 used a weighted 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 granted represents the period of time that we expect them to be outstanding. For the 2002 Plan, we estimated the expected term of options granted based on historical exercise patterns. For the 1989 Plan and 2000 Plan, we estimated the expected term of options granted subsequent to January 1, 2008, based on historical exercise patterns. The expected term for stock options granted prior to January 1, 2008 was a derived output of the simplified method.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

Warrants

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. These warrants expire on April 7, 2011 and can be settled with unregistered shares of our common stock. As of December 31, 2009, 453,267 shares of common stock under the warrants remained outstanding. If we enter into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than us, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares of common stock of the surviving entity as follows:

- if the terms of such merger or acquisition provide for consideration that consists solely of stock of the surviving entity, and the surviving entity has a class of common stock traded on a major national exchange or foreign exchange ("Public Common Shares"), then any replacement warrants issued to the holders will be solely for such publicly traded common shares, at an exchange ratio reflecting the stock consideration paid at the time of such change in control; or

- if the terms of such merger or acquisition shall provide for consideration that consists of cash or a combination of cash and Public Common Shares of the surviving entity, then any replacement warrants issued to the holders will be solely for Public Common Shares of the surviving entity, at an exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of our common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or

- if the surviving entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the warrants may elect, to surrender all outstanding warrants to us in consideration of a cash payment for each share of our common stock subject to purchase under the warrants in an amount equal to 40 percent of the per share cash consideration to be received by a holder of one share of our common stock to be tendered in the merger or acquisition, subject to an aggregate limit of $22,000,000.

In connection with the issuance of the warrants, we entered into a registration rights agreement with Symphony GenIsis Holdings LLC. Pursuant to the registration rights agreement, we filed a registration statement with the SEC covering the shares of common stock issuable upon exercise of the warrants. We are required to use commercially reasonable efforts to maintain the effectiveness of the registration statement over the term of the warrant.

We evaluated the provisions of the Registration Rights Agreement and the Warrant Purchase Agreement and determined that the criteria for equity classification were met; therefore, the warrants were accounted for as part of stockholders' equity.

6. Income Taxes

Primarily as a result of the significant upfront funding that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI in January 2009, we had a substantial amount of taxable income in 2009. To reduce our tax liability, we offset a portion of the taxable income with our 2009 loss from continuing operations. We also used some of our net operating loss carryforwards (NOL's) to reduce our federal income taxes in 2009. The tax law changes that were enacted with the 2008/2009 California Budget suspended our ability to use NOL's to offset our California tax expense for 2009. However, we offset our California income tax liability to the full extent allowed under the tax regulations with our research and development tax credit carryforwards, which California tax regulations limit to 50 percent of our California liability. After using all of our allowable losses and tax credits to reduce our tax liability, our 2009 tax expense was $20.0 million.

We are required to allocate our 2009 tax expense between discontinued operations and continuing operations in our Consolidated Statement of Operations. Accordingly, we have recorded tax expense of $3.2 million in continuing operations and $16.8 million in discontinued operations in 2009.

The expense for income taxes from continuing operations is comprised of (in thousands):

	Year Ended December 31, 2009
Current:	
Federal	$ 2,919
State	4,879
	7,798
Deferred:	
Federal	(1,025)
State	(3,582)
Foreign	—
	(4,607)
Income Tax Expense	$ 3,191

The reconciliation between the Company's effective tax rate on income from continuing operations and the statutory tax rate is as follows (in thousands):

	Year Ended December 31,					
	2009		2008		2007	
Pre tax income	$ (31,765)		$ (14,519)		$ (34,050)	
Statutory rate	(11,118)	35.0%	(5,082)	35.0%	(11,918)	35.0%
State income tax net of federal benefit	(1,825)	5.7%	(834)	5.7%	(1,957)	5.7%
Net change in federal valuation allowance	12,275	(38.6)%	23,182	(159.6)%	(1,704)	5%
Tax credits	3,401	(10.7)%	(7,389)	50.9%	(719)	2.1%
Expired NOL's	(879)	2.8%	(11,514)	79.3%	4,515	(13.2)%
Noncontrolling interest	3,562	(11.2)%	1,918	(13.2)%	9,693	(28.5)%
Other	(2,225)	7.0%	(281)	1.9%	2,090	(6.1)%
Effective rate	$ 3,191	(10.0)%	$ —	—	—	—

We analyze filing positions in all of the federal and state jurisdictions where we are required to file income tax returns, as well as 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. Based on our analysis, we have not recorded any additional tax liability. The total amount of unrecognized tax benefits as of January 1, 2007 was $0. Due to uncertainties surrounding our ability to generate future taxable income to realize these assets, we have established a full valuation to offset our net deferred tax asset. Our practice is to recognize interest and/or penalties related to income tax matters in income tax expense. During the years ended December 31, 2009, 2008 and 2007, we did not recognize any interest or penalties.

We are subject to taxation in the United States and various state jurisdictions. Our tax years for 1993 and forward are subject to examination by the U.S. tax authorities and our tax years for 1989 and forward are subject to examination by the California tax authorities due to the carryforward of unutilized net operating losses and research and development credits. Our tax years for 2001 and 2002 are currently being audited by California's Franchise Tax Board.

Significant components of our deferred tax assets and liabilities as of December 31, 2009 and 2008 are as follows(in thousands):

	Year Ended December 31,	
	2009	2008
Deferred tax assets:		
Net operating loss carryovers	$ 82,378	$ 207,394
R&D Credits	33,130	46,163
Capitalized R&D	30,879	30,374
Deferred Revenue	70,882	9,915
Accrued Restructuring	10,887	10,888
Other	21,696	9,942
Total deferred tax assets	$ 249,852	$ 314,676
Deferred Tax Liabilities:		
Convertible Debt	$ (15,559)	$ (18,345)
Intangible and Capital Assets	(5,879)	(6,578)
Net Deferred Tax Asset	$ 228,414	$ 289,753
Valuation Allowance	(228,414)	(289,753)
Net Deferreds	$ —	$ —

The deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2009 and 2008 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 issued by us. Stockholders' equity will be increased by approximately $24.8 million ($10.1 million, tax effected) if and when such deferred tax assets are ultimately realized. We use tax return ordering for purposes of determining when excess tax benefits have been realized.

At December 31, 2009, we had federal, California and foreign tax net operating loss carryforwards of approximately $232.1 million, $190.5 million and $1.1 million, respectively. The Federal and California tax loss carryforwards will expire at various dates starting in 2014, unless previously utilized. We also had federal and California research and development tax credit carryforwards of approximately $27.4 million and $8.2 million, respectively. The Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless utilized. The California research and development tax credit carryforwards are available indefinitely. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50 percent to 60 percent limitation on the utilization of prior years' California loss carryforwards. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a research relationship. The transaction, which closed in June 2008, 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 at $30 per share, over $1.5 billion in potential milestone payments and a share of profits on mipomersen and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. Under this alliance, Genzyme is responsible for the commercialization of mipomersen. We will contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter, we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme is our preferred partner for the development and commercialization of antisense drugs for certain neurodegenerative and rare diseases.

Genzyme has agreed that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen License and Co-Development Agreement, the first commercial sale of mipomersen or the termination of our mipomersen License and Co-Development Agreement. Thereafter, Genzyme will be

subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen License and Co-Development Agreement or the date Genzyme holds less than 2 percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the fair value of our common stock. Using the Black-Scholes model, we determined that the value of the premium was $100 million, which represents value Genzyme gave to us to help fund the companies' research collaboration that began in January 2008. We are amortizing this premium along with the $175 million licensing fee that we received in the second quarter of 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan. During 2009 and 2008, we recognized revenue of $66.4 million and $48.2 million, respectively, related to the upfront payments we received from Genzyme, which represented 55 percent and 45 percent, respectively, of our total revenue for those years. Our Consolidated Balance Sheet at December 31, 2009 and 2008 included deferred revenue of $160.4 million and $226.8 million, which represents the remaining premium and licensing fee.

Ortho-McNeil-Janssen Pharmaceuticals, Inc., formerly Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs. The collaboration ended and we regained the rights to drugs from both the glucagon receptor and glucocorticoid receptor programs. We intend to move a more potent inhibitor for our GCGR program forward that was identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program.

During 2009, 2008 and 2007, we recognized revenue of $18.4 million, $31.9 million and $13.2 million, respectively, related to the upfront licensing fee, the milestone payment and the research and development funding under this collaboration, which represented 15 percent, 30 percent and 23 percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2008 included deferred revenue of $16.7 million, related to the upfront licensing fee and milestone payment.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin / kexin type 9. Under the terms of the agreement, we received a $15 million upfront licensing fee and are amortizing this amount over the three year period of our performance obligation based on the research plan included in the agreement. Bristol-Myers Squibb agreed to provide us with at least $9 million in research funding over an initial period of three years. In April 2008, Bristol-Myers Squibb designated the first development candidate, BMS-PCSK9$_{Rx}$, resulting from the collaboration for which we earned a $2 million milestone payment. Under the agreement, we will also receive up to $166 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestone payments associated with development of follow-on compounds. Bristol-Myers Squibb will also pay us royalties on sales of products resulting from the collaboration. During 2009, 2008 and 2007, we recognized revenue of $9.1 million, $12.0 million and $5.2 million, respectively, related to the upfront licensing fee, milestone payment and the research funding, which represented 8 percent, 11 percent and 9 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2009 and 2008 included deferred revenue of $1.9 million and $6.7 million, respectively, related to the upfront licensing fee.

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Eli Lilly and Company, which included a joint antisense research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eukaryotic initiation factor-4E. Eli Lilly and Company is responsible for the preclinical and clinical development of LY2181308. As of December 31, 2009, we had earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308. We will receive additional milestone payments aggregating up to $25 million if LY2181308 achieves specified regulatory and commercial milestones, and in addition, royalties on future product sales of this drug.

In December 2009, we reacquired LY2275796, renamed ISIS-eukaryotic initiation factor - 4E$_{Rx}$, and will continue developing the drug. Eli Lilly and Company has the right to reacquire ISIS-eukaryotic initiation factor - 4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development.

During 2009, we earned revenue from our relationship with Eli Lilly and Company totaling $75,000, compared to $156,000 and $402,000 in 2008 and 2007, respectively.

Drug Discovery and Development Satellite Company Collaborations

Achaogen, Inc.

In January 2006, we licensed our proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. In exchange for the exclusive, worldwide license to our aminoglycoside program, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. At the time of receipt, we recognized a valuation allowance of $1.5 million to offset this asset as realization of this asset is uncertain. In January 2009, we received a $1 million milestone payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, as a result of the filing of a investigational new drug, or IND, for Achaogen's aminoglycoside drug, ACHN-490. We have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. At December 31, 2009 and 2008, we owned less than 10 percent of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $33.5 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products. During 2007 and 2008, we did not recognize any revenue from our relationship with Achaogen, compared to $500,000 revenue recognized in 2009, which does not include any revenue from the equity we received from Achaogen.

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a biotechnology company focusing on the discovery, development and commercialization of novel therapeutics to treat human respiratory diseases. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an antisense drug for the treatment of asthma. In November 2009, we participated in Altair's most recent financing, which will fund Altair's Phase 2 development of AIR645. As a result of the financing, our ownership interest in Altair was less than 10 percent at December 31, 2009, compared to approximately 18 percent at December 31, 2008. We have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. In addition to the preferred stock, we will receive additional license fees and royalties from Altair if AIR645 and other drugs arising out of the research collaboration progress. During 2009, 2008 and 2007, we recognized revenue of $79,000, $207,000 and $494,000, respectively, from our relationship with Altair, which does not include any revenue from the equity we received from Altair.

Antisense Therapeutics Limited

In December 2001, we licensed ATL/TV1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL/TV1102 to Teva Pharmaceutical Industries Ltd. As part of our licensing agreement with ATL, we will receive one third of sublicense fees and milestone payments ATL receives from Teva as well as a percentage of any royalties. ATL and Teva reported encouraging data from a Phase 2a study on ATL/TV1102 in patients with relapsing and remitting multiple sclerosis. As a result of our licensing agreement and a milestone payment related to the data that ATL and Teva reported and Teva's decision to continue the development of ATL/TV1102, we earned $1.4 million, which we included in revenue in 2008. In 2009, we earned $2.0 million from Teva for manufacturing ATL/TV1102 drug product.

In addition to ATL/TV1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. ATL pays us cash for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009 we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, we received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering in 2001, representing an initial ownership percentage of approximately 14 percent. The initial ATL common stock we received had a value of $2.8 million, and we recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in our period of performance. At December 31, 2009, our ownership percentage in ATL was approximately 10 percent of ATL's equity, compared to less than 10 percent at December 31, 2008. Our balance sheets at December 31, 2009 and 2008 included a short-term investment at fair market value of $1.8 million and $1.1 million, respectively, related to this equity investment. During 2009, we recorded revenue of $401,000 related to this collaboration compared to $1.6 million and $80,000 for 2008 and 2007, respectively. Our Consolidated Balance Sheets at December 31, 2009 and 2008 included deferred revenue of $210,000 and $232,000, respectively, related to our agreements with ATL.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based company that gastrointestinal drug developers founded in 2006 to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Pharmaceuticals plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis 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. At the time of receipt, we have recognized a valuation allowance of $2 million to offset this asset as realization of this asset is uncertain. At December 31, 2009 and 2008, we owned approximately 13 percent of Atlantic Pharmaceuticals' equity. In addition, assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen. During 2009, 2008 and 2007, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals. Because realization of the upfront equity payment is uncertain, we recorded a full valuation allowance.

Excaliard Pharmaceuticals, 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 have 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 a particular gene target. At the time of receipt, we recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. At December 31, 2009 and 2008, we owned less than 10 percent of Excaliard's equity and we have no remaining performance obligations. In early 2010, we participated in a financing and our ownership in Excaliard remains less than 10 percent. In addition, assuming Excaliard successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $8.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs Excaliard develops, as well as a portion of the fees Excaliard receives if it licenses the drugs. During 2009, 2008 and 2007, we recognized

revenue of $290,000, $384,000 and $1 million, respectively, which does not include any revenue from the equity we received from Excaliard. Our balance sheets at December 31, 2009 and 2008 included deferred revenue of $3,000 and $74,000, respectively, related to our agreements with Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007, a second-generation antisense drug. iCo is initially developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy. iCo paid us a $500,000 upfront fee and will pay us milestone payments totaling up to $22 million for the achievement of clinical and regulatory milestones. In addition, we will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In December 2006, iCo filed an IND application with the Food and Drug Administration for iCo-007 for which we earned a $200,000 milestone payment. In September 2007, iCo initiated Phase 1 clinical trials for iCo-007 and we earned a milestone payment of $1.25 million in the form of 936,875 shares of iCo's common stock. At the time of receipt, we recognized a full valuation allowance to offset the common stock we received as realization of this asset is uncertain.

Over the course of our relationship with iCo, which became a publicly traded company on the Canadian Stock Exchange in 2008, they have paid us in a combination of cash and equity instruments, which included common stock and convertible notes. In February 2009, iCo completed a CAD $1.3 million financing to fund the completion of its Phase 1 clinical study of iCo-007. We participated in the financing and as a result our ownership in iCo at December 31, 2009 was approximately 10 percent, compared to less than 10 percent at December 31, 2008. Our balance sheets at December 31, 2009 and 2008 included a short-term investment at fair market value of $2.1 million and $369,000, respectively, related to this equity investment. Subsequent to the end of the year, we exercised the warrants we held to purchase 1.1 million shares of iCo's common stock and as a result our ownership in iCo at January 31, 2010 was approximately 12 percent. During 2009, we recognized revenue of $14,000 from our relationship with iCo, compared to $7,000 for 2008. During 2007, we did not recognize any revenue from our relationship with iCo.

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement with OncoGenex. In December 2009, OncoGenex licensed OGX-011 to Teva for the treatment of multiple cancer indications. As part of our amended and restated agreement with OncoGenex, 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 milestone payments OncoGenex may receive from Teva in addition to up to 7 percent royalties on sales of OGX-011.

In August 2003, we and OncoGenex entered into a collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2009, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of an additional second-generation antisense anti-cancer drug. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected OGX-427 to develop under the collaboration. OncoGenex paid us an upfront fee of $750,000 with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of the drug. As of December 31, 2009, OncoGenex had not triggered any of the milestone payments related to OGX-427.

In August 2008, OncoGenex completed a reverse takeover of Sonus Pharmaceuticals, a publicly traded company, and became a subsidiary of Sonus, which was renamed OncoGenex Pharmaceuticals, Inc. As a result of this transaction, our shares of OncoGenex preferred stock converted into 122,485 shares of OncoGenex common stock. In December 2008, we recorded a non-cash loss on investment of $1.2 million related to the other-than-temporary impairment of our equity investment in OncoGenex. The loss on investment reflected a decrease in the market value of OncoGenex's stock in 2008, which we believe was primarily a result of the poor financial market conditions. At December 31, 2008, our ownership interest in OncoGenex was less than 10 percent and our balance sheet included a short-term investment at fair market value of $337,000 related to this equity investment. In 2009, OncoGenex's stock began trading significantly above the 2008 levels. As a result, we sold all of the common stock of OncoGenex that we owned for net cash proceeds of $2.8 million in 2009. As of December 31, 2009, we no longer owned any shares of OncoGenex. During 2009, we recognized revenue of $11.4 million from OncoGenex, compared to $4,000 in 2007. During 2008, we did not recognize any revenue from our relationship with OncoGenex.

Technology Development Satellite Company Collaborations

Archemix Corp.

In August 2007, we and Archemix entered into a strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to our technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than targeting messenger RNA. Through this licensing partnership, we are providing access to our oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs based on Archemix's technology. In November 2007, we received a $250,000 milestone payment from Archemix associated with the initiation of Phase 2a trials of their aptamer drug. In May 2009, we received a milestone payment from Archemix related to the advancement of their aptamer drug that incorporates our technology. We will receive a portion of any sublicensing fees Archemix generates as well as milestone payments and royalties on Archemix' drugs that use our technology. During 2009, we recognized $100,000 in revenue from Archemix, compared to $250,000 in 2007. During 2008, we did not recognize any revenue from our relationship with Archemix.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference, or RNA, therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for

double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, the potential milestone payments from Alnylam total $3.4 million, which Alnylam will pay to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of double-stranded RNAi therapeutic targets and, except for the limited license we granted Alnylam in April 2009 described below, all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam at the time of the agreement.

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 RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of December 31, 2009, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of single-stranded RNAi, or ssRNAi, technology. As part of the collaboration, we have co-exclusively licensed our ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to our intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, we and Alnylam also extended our broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million, which we are amortizing over the three year period of our performance obligation based on the research plan included in the agreement. Alnylam will also pay us up to $20 million in additional license fees, which Alnylam will pay in three tranches that include $10 million in 18 months or earlier if *in vivo* efficacy in rodents is demonstrated sooner, $5 million upon achievement of *in vivo* efficacy in non-human primates, and $5 million upon initiation of the first clinical trial with an ssRNAi drug. Alnylam is funding research activities at a minimum of $3 million each year for three years with research and development activities conducted both at Isis and Alnylam. If Alnylam develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, we could potentially receive milestone payments, totaling up to $18.5 million per product, together with royalty payments. Also, initially we are eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam's partnering of ssRNAi products, which will decline over time as Alnylam's investment in the technology and drugs increases. In turn, Alnylam is eligible to receive up to 5 percent of any sublicense payments due to us based on our partnering of ssRNAi products. Both we and Alnylam are eligible to receive royalties from each other on any ssRNAi products developed by the other company. Alnylam has the right to terminate the ssRNAi research program before September 30, 2010, in which event any licenses to ssRNAi products granted by us to Alnylam under the agreement, and any obligation by Alnylam to pay milestone payments, royalties or sublicense payments to us for ssRNAi products under the agreement, would also terminate.

As of December 31, 2009, we had earned a total of $48.1 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics that Alnylam has granted to pharmaceutical partners.

During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2009, we no longer own any shares of Alnylam. During 2009, 2008 and 2007, we generated revenue from our relationship with Alnylam totaling $5.0 million, $4.6 million and $26.5 million, respectively, representing 4 percent, 4 percent and 45 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2009 included deferred revenue of $8.6 million related to our agreement with Alnylam, compared to none at December 31, 2008.

Ercole Biotech, Inc.

In May 2003, we and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative ribonucleic acid, or RNA, splicing. Part of this collaboration included a cross-license of our respective splicing-related intellectual property with Ercole. Under the collaboration, we combined our alternative splicing expertise with Ercole's to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, we granted Ercole a license to our Bcl-x molecule and some of our chemistry patents. Assuming Ercole successfully develops and commercializes a drug incorporating the splicing technology or chemistry we licensed to Ercole, we will receive milestone payments totaling up to $21 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of these drugs. Ercole is solely responsible for the continued development of its drugs.

Similarly, if we successfully develop and commercialize a drug incorporating the splicing technology Ercole licensed to us, we will pay milestone payments to Ercole totaling up to $21 million for the achievement of key clinical, regulatory and sales milestones and will also pay royalties to Ercole on sales of these drugs. We currently do not have a drug incorporating Ercole's technology in clinical development.

In March 2008, AVI BioPharma, Inc. acquired Ercole's rights and obligations under the collaboration agreement. As a result of our collaboration agreement with Ercole, as part of the acquisition, we received a warrant to purchase 238,228 shares of AVI's common stock at an exercise price of $0.1679 per share, and a warrant to purchase 207,757 shares of AVI's common stock at an exercise price of $3.61 per share. During 2009, 2008 and 2007, we did not recognize any revenue from our relationship with Ercole.

Santaris Pharma A/S, formerly Pantheco A/S

In November 1998 and September 2000, we entered into license agreements with Santaris. Under the terms of the license agreements, which the companies amended and restated in May 2003, we licensed our novel antisense chemistry, Peptide Nucleic Acid to Santaris on a limited exclusive basis to

develop products. As part of our original license agreements with Pantheco, we received shares of Pantheco stock. Our ownership interest in Santaris, which was formed in the merger of Pantheco and Cureon A/S, was less than 10 percent at December 31, 2009 and 2008. During 2009, 2008 and 2007, we did not recognize any revenue from our relationship with Santaris.

External Project Funding

CHDI Foundation, Inc.

In November 2007, we entered into an agreement with CHDI, which provides us with up to $9.9 million in funding for the discovery and development of an antisense drug for the treatment of Huntington's disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's disease. If we grant a license to a third party to commercialize our Huntington's disease program, we and CHDI will evenly split the proceeds from the license until CHDI has recouped its funding together with a return determined at a predefined interest rate. Thereafter, we will keep the full amount of any additional proceeds. During 2009, 2008 and 2007, we recognized revenue of $1.7 million, $2.7 million and $329,000, respectively, from our relationship with CHDI.

Symphony GenIsis, Inc.

In April 2006, Symphony Capital formed Symphony GenIsis, capitalized with $75 million, to provide funding for the development of our cholesterol-lowering drug, mipomersen, and two drugs from our metabolic disease program. In this transaction, we licensed to Symphony GenIsis the intellectual property related to these three drug programs. In return, we received an exclusive purchase option from Symphony GenIsis' investors that allowed us to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity.

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of our common stock at an exercise price of $8.93 per share, a 25 percent premium over our 60-day average trading price at the time of the issuance, which was $7.14. As of December 31, 2009, warrants to purchase 453,267 shares remained outstanding. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, we paid structuring and legal fees of $4.1 million.

In September 2007, we exercised our option and purchased the equity of Symphony GenIsis for $120 million, $80.4 million in cash and the remaining amount in approximately 3.4 million shares of our common stock. The $125.3 million on our Consolidated Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis represents a deemed dividend to the previous owners of Symphony GenIsis, a portion of which was non-cash. A portion of the $125.3 million reflects the significant increase in our stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts our net loss attributable to Isis Pharmaceuticals, Inc. common stockholders and our net loss per share calculations for 2007 and does not affect our net loss from continuing or discontinued operations.

Korea Institute of Toxicology

In March 2007, we entered an agreement with the Korea Institute of Toxicology, or KIT. Under the agreement, at our request, KIT will perform toxicology studies on our drugs at reduced preclinical costs in exchange for a nominal royalty. KIT has conducted toxicology and other IND-enabling studies for our ISIS-CRP$_{Rx}$ program, thereby enabling us to initiate a Phase 1 safety study for ISIS-CRP$_{Rx}$ in August 2008. Our relationship with KIT allows for the potential to perform toxicology studies on a number of our other drugs at a significantly reduced cost to us. We are only required to pay KIT when we engage them to perform studies for us.

Michael J. Fox Foundation

In July 2009, we were awarded a grant from the Michael J. Fox Foundation's Therapeutic Development Initiative, which provides us with funding for preclinical research to validate and evaluate a potential antisense target for the treatment of Parkinson's Disease. During 2009, we recognized revenue of $94,000 from our relationship with the Michael J. Fox Foundation.

ALS Association; The Ludwig Institute; Center for Neurological Studies; Muscular Dystrophy Association

In October 2005, we entered 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 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. The researchers from the Ludwig Institute and Center for Neurological Studies, through funding from the ALS Association and the Muscular Dystrophy Association, conducted IND-enabling preclinical studies of ISIS-SOD1$_{Rx}$. The ALS Association and the Muscular Dystrophy Association will provide funding to offset the costs of the Phase 1 study of ISIS-SOD1$_{Rx}$. Except for the funding provided by the ALS Association and the Muscular Dystrophy Association, we control and are responsible for funding the continued development of ISIS-SOD1$_{Rx}$.

Intellectual Property Sale and Licensing Agreements

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 patents and technology, including as it relates to our second generation antisense drugs and to double-stranded small interfering RNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of ribonuclease H patents. In each of 2009 and 2007, we recognized revenue of $10,000 from our relationship with Idera, compared to none for 2008.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from Integrated DNA Technologies, Inc., or IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, we expanded this license agreement to allow us to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees in 2001 and will pay royalties on sales of the drugs utilizing the technology IDT licensed to us.

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

Abbott Molecular Inc.

In January 2008, we and our former subsidiary, Ibis Biosciences, entered into a Strategic Alliance Master Agreement and a Call Option Agreement with AMI. In 2008, AMI invested $40 million in Ibis and we granted AMI an exclusive call option to acquire from us all remaining Ibis capital stock. In December 2008, AMI exercised the call option and we, Ibis and AMI executed a stock purchase agreement. Under the stock purchase agreement, AMI purchased the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. AMI's initial investments totaling $40 million, along with the $175 million AMI paid at closing, resulted in a total acquisition price of $215 million plus the earn out payments described below.

Under the stock purchase agreement, AMI will also pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products from the date of the acquisition closing through December 31, 2025. The earn out payments will equal 5 percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and 3 percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from 5 percent to as low as 2.5 percent and from 3 percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. As part of the acquisition, Ibis distributed to us, immediately prior to the closing, all uncommitted cash and cash equivalents held by Ibis as of the closing.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, now a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in milestone payments, and our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. During 2009, 2008 and 2007, because of our agreement with Drug Royalty Trust 3 as described below we did not recognize any revenue from our relationship with Eyetech.

Drug Royalty Trust 3

In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty Trust 3. To date, we have received a total of $23 million under this arrangement. We and Drug Royalty Trust 3 shared the royalty rights on Macugen from Eyetech through 2009. After 2009, we retain all royalties for Macugen. As a result, we will begin receiving royalties for Macugen in 2010. We retained all milestones payable to us by Eyetech under the license agreement. During 2009 and 2008, we did not recognize any revenue under this arrangement, compared to $7 million in 2007.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. During 2009, 2008 and 2007, we recognized revenue of $1.3 million, $1.2 million and $807,000, respectively, from our relationship with Roche Molecular Systems. Our Consolidated Balance Sheets at December 31, 2009 and 2008 included deferred revenue of $200,000 related to our agreements with Roche Molecular Systems.

Regulus Collaborations

We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. We own 51 percent of Regulus and Alnylam owns the remaining 49 percent. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from a limited liability company to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing. We and Alnylam were the sole and equal investors in the financing. Since we are consolidating the financial results of Regulus, our cash and cash equivalents balance increased by the $10 million Alnylam contributed.

GlaxoSmithKline

In April 2008, Regulus entered into a strategic alliance with GSK to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance utilizes Regulus' expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exercise its option earlier. After exercise of the option, GSK will have an exclusive license to drugs Regulus develops under each program for the relevant microRNA target for further development and commercialization on a

worldwide basis. Regulus will have the right to further develop and commercialize any microRNA therapeutics which GSK chooses not to develop or commercialize.

Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. Regulus is eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In May 2009, Regulus received a $500,000 discovery milestone payment from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. In addition, Regulus would receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

Regulus is amortizing the $15 million option fee into revenue over Regulus' six year period of performance. We show the $5 million note as a liability on our Consolidated Balance Sheet. During 2009 and 2008, Regulus recognized revenue of $3.0 million and $1.9 million, respectively, related to Regulus' collaboration with GSK. Our balance sheet at December 31, 2009 and 2008 included deferred revenue of $10.6 million and $13.1 million, respectively, related to Regulus' collaboration with GSK.

In February 2010, Regulus announced the establishment of a new worldwide strategic alliance with GSK to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for the treatment of hepatitis C virus, or HCV, infection. The new HCV alliance expands the ongoing GSK-Regulus immuno-inflammatory disease alliance formed in 2008. Under the terms of the new collaboration, Regulus will receive additional upfront and early stage milestone payments with the potential to earn more than $150 million in miR-122-related combined payments, and tiered royalties up to double digits on worldwide sales.

Under the terms of the HCV collaboration, Regulus will receive $8 million from GSK, including a $3 million license fee and a second $5 million note (guaranteed by Isis and Alnylam) that will convert into Regulus common stock in the future under certain specified circumstances. In addition, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestone payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

As part of the HCV collaboration, Regulus granted GSK a limited license to develop and commercialize the miR-122 antagonist SPC 3649, if GSK acquires rights to this compound. Regulus will receive development and regulatory milestones as well as royalties if GSK develops and commercializes SPC 3649.

8. Segment Information and Concentration of Business Risk

Segment Information

Prior to AMI's acquisition of our Ibis business, we reported our financial results in three segments. We currently report our financial results in two segments, Drug Discovery and Development and Regulus. Segment loss from operations includes revenue less research and development expenses and general and administrative expenses attributable to each segment.

Our Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestone payments and royalties or profit sharing payments. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Regulus segment generates revenue from research grants and collaborations with corporate partners such as its strategic alliance with GSK.

The following is segment information for the years ended December 31, 2009, 2008 and 2007 (in thousands).

Year ended December 31, 2009	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 105,118	$ 3,013	$ 108,131
Licensing and royalty	13,469	—	13,469
Total segment revenue	$ 118,587	$ 3,013	$ 121,600
Loss from operations	$ (18,815)	$ (8,723)	$ (27,538)
Total assets as of December 31, 2009	$ 634,820	$ 22,364	$ 657,184

Year ended December 31, 2008	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 96,743	$ 2,110	$ 98,853
Licensing and royalty	8,337	—	8,337

Total segment revenue	$ 105,080	$ 2,110	$ 107,190
Loss from operations	$ (5,139)	$ (7,921)	$ (13,060)
Total assets as of December 31, 2008 (1)	$ 533,637	$ 23,677	$ 557,314

Year ended December 31, 2007	Drug Discovery and Development	Corporate	Total
Revenue:			
Research and development	$ 22,200	$ 119	$ 22,319
Licensing and royalty	36,025	—	36,025
Total segment revenue	$ 58,225	$ 119	$ 58,344
Loss from operations	$ (32,014)	$ (905)	$ (32,919)

(1) Total assets do not include $15.5 million of assets from discontinued operations as of December 31, 2008.

Concentrations 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:

	2009	2008	2007
Partner A	55%	45%	0%
Partner B	15%	30%	23%
Partner C	8%	11%	9%
Partner D	4%	4%	45%
Partner E	0%	0%	12%

Contract receivables from one significant partner comprised approximately 92 percent of contract receivables at December 31, 2009. Contract receivables from three significant partners comprised approximately 25 percent, 18 percent and 14 percent of contract receivables at December 31, 2008.

9. Employee Post 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 ($16,500 and $22,000 in 2009 for employees under 50 years old and over 50 years old, respectively). We made approximately $450,000, $467,000 and $414,000 in matching contributions for the years ended December 31, 2009, 2008 and 2007, respectively.

10. Legal Proceedings

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery remains in its early stage. As such, we have no basis on which to predict or record a loss related to this claim as of December 31, 2009. We will continue to represent and defend Ibis Biosciences in this matter.

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, 2009, and 2008 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2009 Quarters				
Revenue	$ 31,576	$ 30,992	$ 26,771	$ 32,261
Operating expenses	32,218	35,819	37,167	43,934
Loss from operations	(642)	(4,827)	(10,396)	(11,673)
Net income (loss)	185,305	(3,587)	(12,718)	(18,328)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 186,218	$ (2,730)	$ (11,582)	$ (16,840)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(2)	$ 1.91	$ (0.03)	$ (0.12)	$ (0.17)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2008 Quarters				
Revenue(1)	$ 18,375	$ 29,703	$ 29,463	$ 29,649
Operating expenses(1)	24,616	28,622	29,287	37,725
Income (loss) from operations(1)	(6,241)	1,081	176	(8,076)
Net income (loss)(3)	(6,669)	(4,702)	405	(11,940)

Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(3)	$ (5,785)	$ (3,737)	$ 1,613	$ (10,263)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(2)(3)	$ (0.06)	$ (0.04)	$ 0.02	$ (0.11)

(1) As a result of the sale of Ibis to AMI, we have adjusted our revenue, operating expenses, and income (loss) from operations to reflect Ibis' results of operations as discontinued operations for all prior periods.

(2) We computed net 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.

(3) We have adjusted our net income (loss), net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders and the related per share information in 2008 to reflect the required retroactive adoption of accounting standards. See Note 1, *Organization and Significant Accounting Policies*, for additional details.

During the preparation of the annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we have revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The table below shows the impact by quarter on the statement of operations lines impacted (in thousands, except per share data).

	As Originally Reported	As Adjusted	Effect of Change
For the quarter ended March 31, 2009:			
Loss from continuing operations, before income tax benefit (expense)	$ (1,531)	$ (1,531)	$ —
Income tax benefit (expense)	$ 717	$ (160)	$ (877)
Net loss from continuing operations, including income tax benefit (expense)	$ (814)	$ (1,691)	$ (877)
Net income from discontinued operations, net of tax	$ 171,744	$ 186,996	$ 15,252
Net income	$ 170,930	$ 185,305	$ 14,375
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	$ 913	$ 913	$ —
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 171,843	$ 186,218	$ 14,375
Basic net income (loss) per share:			
Net income (loss) from continuing operations	$ —	$ (0.01)	$ (0.01)
Net income from discontinued operations	$ 1.76	$ 1.92	$ 0.16
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1.76	$ 1.91	$ 0.15
Diluted net income (loss) per share:			
Net income (loss) from continuing operations	$ 0.03	$ (0.01)	$ (0.04)
Net income from discontinued operations	$ 1.54	$ 1.92	$ 0.38
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1.57	$ 1.91	$ 0.34
For the quarter ended June 30, 2009:			
Loss from continuing operations, before income tax benefit (expense)	$ (3,692)	$ (3,692)	$ —
Income tax benefit (expense)	$ (61)	$ 11	$ 72
Net loss from continuing operations, including income tax benefit (expense)	$ (3,753)	$ (3,681)	$ 72
Net income from discontinued operations, net of tax	$ —	$ 94	$ 94
Net loss	$ (3,753)	$ (3,587)	$ 166
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	$ 857	$ 857	$ —
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,896)	$ (2,730)	$ 166
Basic and diluted net loss per share:			
Net loss from continuing operations	$ (0.03)	$ (0.03)	$ —
Net income from discontinued operations	$ —	$ —	$ —
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.03)	$ (0.03)	$ —
For the quarter ended September 30, 2009:			
Loss from continuing operations, before income tax benefit (expense)	$ (12,028)	$ (12,028)	$ —
Income tax benefit (expense)	$ 3,968	$ (724)	$ (4,692)
Net loss from continuing operations, including income tax benefit (expense)	$ (8,060)	$ (12,752)	$ (4,692)
Net income from discontinued operations, net of tax	$ —	$ 34	$ 34
Net loss	$ (8,060)	$ (12,718)	$ (4,658)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	$ 1,136	$ 1,136	$ —
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (6,924)	$ (11,582)	$ (4,658)
Basic and diluted net loss per share:			
Net loss from continuing operations	$ (0.07)	$ (0.12)	$ (0.05)
Net income from discontinued operations	$ —	$ —	$
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.07)	$ (0.12)	$ (0.05)

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

DRUG DEVELOPMENT AND LICENSE OPTION AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

December 2, 2009

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

DRUG DEVELOPMENT AND LICENSE OPTION AGREEMENT

THIS DRUG DEVELOPMENT AND LICENSE OPTION AGREEMENT (the ***"Agreement"***) executed on December 2, 2009 (the ***"Effective Date"***), by and between **ELI LILLY AND COMPANY**, a corporation organized and existing under the laws of Indiana and its Affiliates (together, ***"Lilly"***), and **ISIS PHARMACEUTICALS, INC.**, a corporation organized and existing under the laws of Delaware and its Affiliates (together, ***"Isis"***).

RECITALS

A. Lilly and Isis are parties to the Second Amended and Restated Collaboration Agreement dated August 5, 2005 (the ***"Collaboration Agreement"***) to identify, characterize and/or develop antisense oligonucleotides that modulate the expression of biological molecules and to characterize the effect of such modulation to validate gene targets for drug discovery, including antisense drug discovery;

B. Under the Collaboration Agreement, the Parties conducted research and development on ASO Compounds directed against eIF-4E, which resulted in the development of the Product by Lilly;

C. Lilly now wishes to return the eIF-4E Program, including the Product, to Isis so that Isis may continue developing the Product and the eIF-4E Program;

D. In return, Isis will pay Lilly a technology transfer fee and royalties on the Product and will grant Lilly an option to later re-acquire a license to the eIF-4E Program, including the Product on certain pre-defined terms.

E. Except for the return of the eIF-4E Program and the Product to Isis and related matters, this Agreement is not intended to modify or amend the Collaboration Agreement, which shall continue in effect following the execution of this Agreement.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained in this Agreement, the Parties agree as follows:

ARTICLE 1

DEFINITIONS; AMENDMENT AND RESTATEMENT

1.1 **Definitions.** Capitalized terms used in this Agreement, whether in the singular or plural, have the meanings set forth in Schedule 1.1 which is attached hereto and made part of this Agreement, or as otherwise specifically defined in this Agreement.

ARTICLE 2

TERMINATION OF LILLY'S RIGHTS IN PRODUCT; TECHNOLOGY TRANSFER

2.1 **Termination.** Lilly's license and other rights under the Collaboration Agreement with respect to the eIF-4E Program and the Product are hereby terminated, and all rights granted to Lilly under the Collaboration Agreement with respect to the eIF-4E Program and to the Product are returned to Isis. Except as specifically stated in this Agreement: (i) the Collaboration Agreement and any license granted to Lilly thereunder with respect to any ASO Compounds or ASO Products, in each case that are not the Product or part of the eIF-4E Program, will remain in full force and effect, and (ii) neither Lilly nor Isis will have any further obligation with respect to the eIF4E Program or the Product.

2.2 **Patent Assignment.** Lilly hereby assigns and transfers, to Isis, all of Lilly's rights, title, and interests in and to the Lilly Product Patents. Simultaneously with the execution of this Agreement, Lilly will execute and deliver a confirmatory assignment relating to all Lilly Product Patents, in the form of the assignment attached hereto as ***Schedule D***.

2.3 **Transfer of Records.** Lilly and Isis will, promptly following the Effective Date, agree to and complete an appropriate process for transfer of information under Lilly's control (subject to receipt of any necessary Third Party consents) relating to the eIF-4E Program and the Product that will include, to the extent practicable and reasonably useful to Isis, (a) all batch records related to the Product, including but not limited to corresponding release data; (b) toxicity and pharmacokinetic data and reports related to the Product; (c) pharmacology data and reports related to the Product; (d) Product characterization data, (e) Product stability data; (f) any other records, including, but not limited to, raw data or interim or final reports, related to the Product; and (h) all Regulatory Documents, in each case that are in the possession of Lilly or its Affiliates, or, to the extent Lilly controls the same, any Third Party engaged by Lilly or any of its Affiliates. Lilly will use its good faith efforts to complete such transfer within [***] days following the Effective Date. Lilly may retain copies of all such materials for archival purposes.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

ARTICLE 3

DEVELOPMENT AND COMMERCIALIZATION; REPORTING

3.1 **Phase I Study.** Lilly, [***], will use its commercially reasonable efforts to promptly complete the Ongoing Phase I Study, including but not limited to completing patient follow-up, data collection, data analyses, summary reports and final reports. Lilly will transfer to Isis the results generated under the Ongoing Phase I Study promptly after they become available to Lilly from the Third Party vendor assembling such data and reports, including, but not limited to, raw data, interim and final reports in a manner consistent with Section 2.3. Lilly will use its good faith efforts to (i) send Isis the raw data collected by Lilly (in the format collected by Lilly) from such Phase I Study within [***] days following the locking of the primary database for such study, and (ii) send Isis the clinical summary reports for such Phase I Study within [***] days following the locking of the primary database for such study. Except for as provided in Article 4, Lilly shall have no obligation to conduct any other development activities with respect to the eIF-4E Program or the Product.

3.2 **Development and Commercialization.**

3.2.1 Except for Lilly's obligation to complete the Ongoing Phase I Study as set forth in Section 3.1 above, Isis will be solely responsible (without obligation except as set forth in Section 3.2.2) for all development and commercialization activities relating to the Product and the eIF-4E Program; *provided*, Isis will not be required to assume any contracts or obligations Lilly has with a Third Party related to the Product. Within [***] days following the Effective Date, Isis shall notify Lilly of any Third Party contracts Isis desires to assume. Lilly will use its good faith efforts to assist Isis in assuming such contracts, but will not be obligated to pay any money or incur any continuing obligation under such contracts. Lilly shall be free to terminate any contract that Isis does not assume. Lilly will cooperate with Isis to assign (or otherwise transfer responsibility) under any Regulatory Document that is necessary for Isis to conduct the activities described in this Section 3.2; provided, Lilly will use its good faith efforts to transfer to Isis ownership of the IND for the Product by [***]. Thereafter, Isis will have the sole right and responsibility for the preparation of any regulatory filings required in order to conduct clinical trials on the Product in the Territory, together with the preparation of suitable applications for marketing approval in the Territory and will be the owner and party of record of all such regulatory filings. All protocols for clinical trials conducted by Isis prior to the exercise or expiration of the Lilly option provided for in Section 5.1 shall be approved by the applicable Institutional Review Board and submitted to the applicable Regulatory Authority.

3.2.2 Isis will use its commercially reasonable efforts to conduct at [***]; *provided*, Isis may discontinue such development (and will not be required to conduct [***] for the Product) if at any time Isis in good faith believes that continuing such development (i) is not warranted because the Product has not demonstrated [***], or (ii) would pose an unacceptable risk or threat of harm in humans; or (iii) would violate any applicable law, ethical principles, or principles of scientific integrity.

CONFIDENTIAL TREATMENT REQUESTED
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3.3 **Progress Reports.** Isis will provide Lilly with [***] written reports describing in reasonable detail the research, development and commercialization activities by Isis for the Product conducted in the previous [***]. In addition, Isis will provide Lilly a copy of the final study report for any clinical studies of the Product within [***] days of the date the same becomes available to Isis.

3.4 **Compliance.** All studies done under this Agreement will be carried out in compliance with any applicable laws, regulations, or guidelines governing the conduct of research at the site where such studies are being conducted. All animals involved in studies under this Agreement will be provided humane care and treatment in accordance with generally acceptable current veterinary practices.

ARTICLE 4

MANUFACTURING AND SUPPLY

4.1 **Supply of Existing Material.** To the extent the same is available to Lilly from its existing supplies of manufactured material, Lilly will supply Isis with up to [***] of the existing API for the Product which was produced in accordance with cGMP and is located at Lilly's facilities as of the Effective Date (***"Lilly API"***). Isis agrees to purchase the Lilly API, on the terms set forth in this ARTICLE 4. Lilly will endeavor to [***] on or before [***] (the ***"[***]"***). Lilly will perform the [***] in accordance with the [***] attached hereto as Schedule E (the ***"[***]"***). Lilly will use good faith efforts to update the [***] within [***] days of the Effective Date to include a [***] timeline for the [***], including a [***]. Lilly will update Isis,

every [***] (or on a [***] basis if mutually agreed by the Parties' quality groups) regarding Lilly's progress in performing the [***], and Lilly will immediately notify Isis if Lilly decides to [***]. Notwithstanding the foregoing, Isis, at its election, will not be required to purchase the material from Lilly if (i) Lilly has not [***], or if Lilly notifies Isis that Lilly [***], which Lilly may do if Lilly in good faith concludes that [***]; or (ii) less than [***] grams of API for the Product is [***]. Lilly makes no representation or warranty that any particular quantity of the Lilly API will be available or that any of Lilly API will [***].

4.2 **Transfer of other Information.** Lilly will also use its good faith efforts to provide any existing information and documentation on such Lilly API within Lilly's control (and subject to receipt of any necessary Third Party consents) that is requested by Isis and that is required by, or useful to, regulatory authorities at [***] to Isis, including, but not limited to: summaries of [***] and all [***] records for the Lilly API, the information specified in the [***], as well as Lilly's [***] for the Product; *provided, however*, that Lilly will not be required to create any such documentation for Isis, unless otherwise agreed by the Parties. Lilly will also use its good faith efforts to assist Isis in obtaining information controlled by the manufacturer (the ***"Lilly CMO"***) of the Lilly API; and in obtaining the right to [***] of the Lilly CMO. Except as explicitly provided as part of the [***], Isis acknowledges that the Lilly API is provided "AS IS," without any warranty of any kind,

express or implied, including any warranty of merchantability or fitness for a particular purpose.

4.3 **Lilly API Price.** Isis will pay Lilly US$[***] per gram (inclusive of all shipping, freight and other delivery charges, the ***"API Price"***) for the Lilly API; *provided*, that if [***] does not occur by [***], then the API Price will automatically [***] at the rate of [***] per gram for each [***] day period between the date of the [***] and the [***]. In addition, if Lilly does not complete the [***] by [***], then Isis will have the rights further set forth in [***] of this Agreement and, if applicable [***] of the Form License Agreement.

4.4 **[***].** If, in Isis' reasonable opinion, differences in the [***] in the Lilly API cause Isis to [***], Isis may [***] the [***] of the [***] against the [***] of the [***]. Additionally, if Isis reasonably believes it is necessary to [***] the [***] to comply with applicable law or satisfy the requirements of any Regulatory Authority, and such [***] consents to the same, Isis may also offset [***] of each [***] against the [***] of the [***]. If Isis is entitled to an [***] under this Section 4.4, but the [***] amount of the [***] for the [***] is less than the amount Isis is [***] to [***] under this Section 4.4, then, at Isis' written election, Lilly will [***] to Isis an [***]of the [***] Isis [***] that is equal to the [***]. In no event, however, will Lilly be obligated to [***] an [***] greater than $[***]. Isis will provide Lilly with reasonable documentation regarding any [***] Isis [***] under this Section 4.4.

4.5. **Isis Manufacturing Arrangements.** Isis shall include in any agreement between Isis and a Third Party relating to manufacturing process development or manufacture of Product appropriate provisions to ensure that Isis retains ownership of and access to all manufacturing know-how or other intellectual property, with the right to transfer the same to Lilly without cost to Lilly in the event Lilly exercises its option to acquire rights to the Product. Isis shall ensure that any such agreements, to the extent they would extend beyond the date on which Lilly may exercise its option, are [***] at [***] by Lilly without [***], and do not contain any terms that would [***] Lilly's efforts to manufacture Product following exercise of the Lilly option.

ARTICLE 5

LILLY OPTION

5.1 **Grant of Option.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an exclusive (except as permitted by Section 6.1) option to obtain an exclusive, royalty-bearing license, to develop, make, use, import, offer for sale and sell the Product, and the ASO Compounds in the eIF4-E Program on the terms and conditions set forth in the form of license agreement attached hereto as ***Schedule A*** (the ***"Form License Agreement"***). During the term of Lilly's option under this Section 5.1, Isis shall not grant any rights in the Product, the ASO Compounds or the eIF4-E Program to any other person that would be inconsistent with Lilly's right to exercise such option.

5.2 **Exercise of Option.**

5.2.1 Lilly's option under Section 5.1 with respect to Products that would require Lilly to pay a license fee and milestones at Tier 1 Rates under the Form License Agreement is exercisable at any time before the earlier of (a) [***] for the Product; and (b) the [***], in accordance with ARTICLE 6 below. Lilly's option under Section 5.1 that would require Lilly to pay a license fee and milestones at Tier 2 Rates or Tier 3 Rates under the Form License Agreement is exercisable after Isis has [***] of its planned [***] for the Product, but before the earlier of (y) the [***] for the Product; and (z) the [***], in accordance with ARTICLE 6 below. Isis will provide Lilly at least [***] days advance written notice of the Phase III Study Initiation for the Product. Isis will provide Lilly with written notice promptly following the date Isis has [***] of its planned [***] for the Product.

5.2.2 Prior to exercising its option, Lilly may, upon [***] days prior notice to Isis, have access to all available information regarding the Product, and the eIF-4E Program and access to Isis personnel so that Lilly conduct a reasonable and customary due diligence investigation; provided, such diligence is part of Lilly's good faith consideration of whether to exercise its option, and such diligence has been approved in accordance with Lilly's normal due diligence sanction procedures. Lilly may exercise the option granted pursuant to this ARTICLE 5 by providing written notice to Isis prior to the option's expiration. The date that Isis timely receives such notice will be deemed the ***"Option Exercise Notice Date."*** The Form License Agreement will be deemed granted to Lilly on the Option Exercise Notice Date.

5.3 **Automatic Termination.** Except as set forth in Section 5.4 below, If Lilly fails to timely exercise its option prior to the earlier of (a) the [***] for the Product; and (b) the [***], in accordance with ARTICLE 6 below, then the option granted under this ARTICLE 5 will automatically expire and terminate.

5.4 **Substitute Option.** In the event (i) Isis discontinues development of Product [***], (ii) Lilly has not previously exercised its option with respect to Product, and (iii) within [***] years after the date on which Isis discontinues development of Product, Isis initiates human clinical trials of any other ASO Compound targeting the eIF-4E mechanism, Lilly shall have the option to acquire a license to such other ASO Compound upon the same terms as were applicable to Lilly's option to acquire the Product.

ARTICLE 6
LILLY RIGHT OF FIRST NEGOTIATION

6.1 Notwithstanding Section 5.1 above, once (a) Isis has publicly disclosed the data or a summary of the results of [***] for the Product; and (b) Isis has complied with the terms and conditions of the Lilly Right of First Negotiation set forth below in this ARTICLE 6, then Isis may execute a license with a development and commercialization partner for the Product and the eIF-4E Program.

6.2 **Lilly's Right of First Negotiation.** Isis hereby grants to Lilly a right of first negotiation (the ***"Lilly Right of First Negotiation"***) to obtain from Isis an exclusive, worldwide, license to develop and commercialize the eIF4-E Program, including the Product according to the provisions set forth in this ARTICLE 6.

6.3 Once Isis has publicly disclosed the data or a summary of the results [***] for the Product, and if Isis intends to [***] of the Product, Isis will so notify Lilly in writing (the ***"Isis Notification"***). The Isis Notification will include summaries of preclinical, toxicological and available clinical data and patent information of the level of detail included in a Clinical Investigators Brochure. All information contained in the Isis Notification or provided pursuant to the due diligence investigation contemplated by the next sentence will be considered Confidential Information of Isis and subject to ARTICLE 8 and will be used by Lilly solely for the purpose of evaluating its interest in exercising its rights under this ARTICLE 6. After receipt of the Isis Notification, Lilly may, upon [***] days prior notice to Isis, have access to [***] available information regarding the Product and access to Isis personnel so that Lilly conduct a customary due diligence investigation.

6.4 Within [***] days after receipt of the Isis Notification (the ***"Lilly Response Period"***), Lilly will either (i) notify Isis that Lilly is interested in the Product, including a written proposal of the terms that Lilly intends to form the basis of a final agreement for the development and commercialization of the Product (a ***"Lilly Expression of Interest"***); or (ii) exercise its Product option to the extent permitted under ARTICLE 5 above; or (iii) notify Isis that Lilly has no interest in the development and commercialization of the Product.

6.5 If Lilly provides Isis with a Lilly Expression of Interest prior to the termination of the Lilly Response Period, then the Parties will negotiate exclusively in good faith reasonable terms that are intended to form the basis of a final agreement for a period of up to [***] days from the date of Lilly's Expression of Interest.

6.6 If, (i) Lilly fails to provide Isis with a Lilly Expression of Interest or exercise its option prior to the termination of the Lilly Response Period; or (ii) Lilly notifies Isis that Lilly has no interest in the development and commercialization of the Product; or (iii) despite good faith negotiations, Lilly and Isis are unable to reach an agreement by the [***] day following Isis' receipt of a Lilly Expression of Interest; then, in each case, Isis will thereafter be free to develop the Product on its own or execute a license with an alternative partners with respect to the development and commercialization of the Product; *provided, however,* that in the event of (iii) of this Section 6.6, then Lilly shall have a period of [***] days following the [***] day in which to exercise its option. If during such period Lilly does not exercise its option, then Isis may, subject to Section 6.9, seek an alternative partner, and where Isis intends to execute a license with an alternative partner, the following provisions will apply:

6.6.1 milestone payments and upfront license fees offered by any Third Party and accepted by Isis for the Product must exceed (on a net present value basis) those set forth in the Lilly's last written proposal by [***] percent ([***]%). The discount rate for the net present value calculation will be the prime rate published in the Wall Street Journal (print or Internet addition) at the time of negotiation plus [***] percent ([***]%). For the

purpose of calculating net present value under this Section 6.6 the following timing definitions will apply: (i) Phase III Study Initiation will be considered to begin [***] years after the [***] Study Initiation; (ii) Registration Submission will be considered to occur [***] years from Phase III Study Initiation; and (iii) First Commercial Sale will be considered to occur [***] year after Registration submission.

6.6.2 Royalty rates offered by any Third Party must equal or exceed [***]% multiplied by the royalty rate set forth in the last written terms offered by Lilly.

6.6.3. All other terms and conditions of the third party offer, taken as a whole, are not materially worse than those terms and conditions offered by Lilly.

6.7 Isis will [***] the terms of any such proposed Third Party agreement to [***], and in the event that Lilly in good faith disputes that such terms meet the requirements of Section 6.6, then an independent Third Party with the requisite expertise, selected by the Parties, will make such

determination. The expense of such independent Third Party will be shared equally by the Parties. In the event that any Third Party terms include non-monetary consideration (e.g., licensing of patent rights), then such independent Third Party will value such non-monetary consideration as well as any other terms offered by such Third Party and decide whether as a whole the Third Party offer exceeds the Lilly offer as set forth above.

6.8 If a Third Party offer for the Isis Product exceeds the last written terms offered by Lilly by the guidelines outlined in Section 6.6 and is accepted by Isis, Lilly will still be entitled to receive from Isis the running royalty in accordance with Section 7.2 below. .

6.9 If Lilly provides Isis with a timely Lilly Expression of Interest, pursuant to Section 6.5, but Isis does not enter into an agreement with Lilly or reach a mutually agreed-upon term sheet that represents a [***] from a Third Party approved by an officer of the company of such Third Party with respect to the development and commercialization of the Product pursuant to the provisions of Section 6.6 on or before the date Isis publicly announces [***] or a [***] of [***] of a [***] for the Product (i.e. where Isis has not previously publicly announced any [***] from such [***]), then the Lilly Right of First Negotiation with respect to such Product will be revived. For purposes of clarity, if the Lilly Right of First Negotiation is not revived under this Section 6.9 because there was a mutually agreed-upon term sheet that represents a [***] from a Third Party approved by an officer of the company of such Third Party, then, if the transaction contemplated by such term sheet is later abandoned by Isis and such Third Party, then the Lilly Right of First Negotiation will be revived following the date of such abandonment.

6.10 Notwithstanding the other provisions of this ARTICLE 6, the Lilly Right of First Negotiation will automatically expire and terminate upon the exercise or expiration of Lilly's option under ARTICLE 5.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

ARTICLE 7
PAYMENTS AND ACCOUNTING

7.1 **Technology Access Fee**. In consideration for the patent assignment and technology transfer set forth in Sections 2.2 and 2.3 above, Isis will pay Lilly $[***] within 5 business days following the Effective Date.

7.2 **Royalties.** Isis will pay to Lilly a royalty equal to [***]% of the Net Sales of the Product by Isis, its Affiliates or Licensees, on a country-by-country basis from the date of the First Commercial Sale of the Product in such country until the expiration of the last to expire claim within the Product Patents that Covers the [***] of [***] or [***] of [***] of such Product in such country. Notwithstanding the foregoing, if Lilly does not complete the [***] by [***], then Isis will not be required to pay royalties on the Net Sales of the Product by Isis its Affiliates or Licensees that occur during the first [***] months following the First Commercial Sale of the Product.

7.3 **Third Party Royalty Obligations.** Isis shall be responsible for payment of all third party royalty and other financial obligations with respect to sales of Product under any present or future license arrangements, unless such obligations were created by Lilly.

7.4 **Accounting Reports; Payment of Royalty.** Isis (including its Affiliates) and its Licensees under the Product Patents will keep complete and accurate books and records which may be necessary to ascertain properly and to verify the payments owed hereunder. Isis will make royalty payments to Lilly for Products sold by Isis, its Affiliates and Licensees during the Calendar Quarter within ninety (90) days of the last day of that Calendar Quarter. Each royalty payment will be accompanied by a written report for that Calendar Quarter showing the Net Sales of the Product sold by Isis, worldwide during the quarterly reporting period and the calculation of the royalties payable under this Agreement.

7.5 **Audits.** Upon Lilly's written request, and not more than once in each Calendar Year, Isis will permit Lilly's independent certified public accountant to have access during normal business hours to such of Isis' records as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the current year and the preceding [***] years prior to the date of such request. Lilly will submit an audit plan, including audit scope, to Isis for Isis' approval, which will not be unreasonably withheld, prior to audit implementation. The independent certified public accountants will keep confidential any information obtained during such inspection and will report to Lilly only the amounts of Net Sales and royalties due and payable. Upon the expiration of [***] years following the end of any Calendar Year, the calculation of royalties payable with respect to such year will be binding and conclusive upon Lilly, and Isis and its Affiliates and Licensees will be released from any liability or accountability with respect to royalties for such year. If such accounting firm concludes that additional royalties were owed, or that Isis overpaid royalties, during such period, Isis will pay the additional royalties, or Lilly will return any overpaid royalties, within ninety (90) days of the date Lilly delivers to Isis such accounting firm's written report. The fees charged by such accounting firm will be paid by Lilly unless the additional royalties owed by Isis exceed [***] percent ([***]%) of the royalties paid for the royalty period subject to the audit, in which case Isis will pay the reasonable fees of the accounting firm. Isis will include in each license granted by it under the Product Patents a provision requiring the Licensee to make [***] to Isis, to [***] and [***] records of sales made pursuant to such license and to [***] to such records by a mutually agreed upon [***] to the same extent

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required of Isis under this Agreement. Lilly will treat all financial information subject to review under this Section 7.5 or under any license agreement in accordance with the confidentiality provisions of this Agreement, and will cause its accounting firm to enter into an acceptable confidentiality agreement with Isis obligating such firm to retain all such financial information in confidence pursuant to such confidentiality agreement.

7.6 **Payment.** All payments to Lilly under this Agreement will be made in United States Dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by Lilly from time to time. Isis will pay a late payment service charge of [***]% per month (or the highest amount allowed by law, if lower than [***]%) on all past-due amounts owed by Isis under this Agreement.

7.7 **Income Tax Withholding.** Lilly will be responsible for its own tax liabilities resulting from the payments received from Isis under this Agreement. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this ARTICLE 7, Isis will make such withholding payments as required and subtract such withholding payments from the payments set forth in this ARTICLE 7. Isis will submit appropriate proof of payment of the withholding taxes to Lilly within a reasonable period of time.

ARTICLE 8

CONFIDENTIALITY

8.1 **Nondisclosure and Nonuse Obligations.** All Confidential Information disclosed by one Party to the other Party hereunder will be maintained in confidence and will not be disclosed to any Third Party or used for any purpose except as expressly permitted herein without the prior written consent of the other Party.

8.2 **Permitted Disclosure of Confidential Information.** Notwithstanding Section 8.1, a Party may disclose Confidential Information of the other Party as follows:

8.2.1 to appropriate U.S. and/or foreign tax authorities, appropriate patent agencies in order to obtain Patent Rights pursuant to this Agreement, appropriate Regulatory Authorities to gain approval to conduct clinical trials or to market Products pursuant to this Agreement, but such disclosure, may be only to the extent reasonably necessary to obtain such Patent Rights, authorizations or approvals;

8.2.2 if required by any governmental authority other than under Section 8.2.1, provided that prior to such disclosure, the Party subject to the request for such disclosure (the ***"Notifying Party"***) promptly notifies the other Party of such requirement so that such other Party may seek a protective order or other appropriate remedy; and *provided, further*, that in the event that no such protective order or other remedy is obtained, or that such other Party waives compliance with this ARTICLE 8, the Notifying Party will furnish only that portion of the other Party's Confidential Information that it is advised by counsel it is legally required to furnish and will exercise all reasonable efforts to obtain reasonable assurance that

confidential treatment will be accorded the other Party's Confidential Information so furnished;

8.2.3 by a Party to its permitted Licensees, agents, consultants, Affiliates and/or other Third Parties for the research and development, manufacturing and/or marketing of the Product (or for such Parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Affiliates and Third Parties agree to be bound by the confidentiality and non-use obligations contained in this Agreement; or

8.2.4 if required to be disclosed by law or court order, provided that notice is promptly delivered to the non-disclosing Party in order to provide an opportunity to challenge or limit the disclosure obligations.

ARTICLE 9

DISCLAIMERS, REPRESENTATIONS, WARRANTIES AND INDEMNIFICATIONS

9.1 **Lilly Representations and Warranties.** Lilly represents and warrants to Isis as follows:

9.1.1 **Corporate Existence and Authority.** As of the Effective Date, Lilly: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated; (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement, including the right to grant the patent assignments and transfer the technology hereunder; (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder; (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder; and (e) has delivered an Agreement that has been duly executed and constitutes a legal, valid, binding obligation of Lilly and is enforceable against it in accordance with its terms;

9.1.2 **Patents, Prior Art.** As of the Effective Date and to the best of Lilly' knowledge, it has the sufficient legal and/or beneficial title and ownership under the Lilly Product Patents as is necessary to grant the patent assignments to Isis pursuant to this Agreement;

9.1.3 **Absence of Litigation, Infringement, Misappropriation**. As of the Effective Date and to the best of Lilly' knowledge, there is no pending litigation against Lilly (nor has Lilly received any written communication) which alleges that Lilly' activities in developing the Product have or would infringe or misappropriate any intellectual property rights of any Third Party;

9.1.4 **Third Party Obligations**. As of the Effective Date, Lilly is not a party to an agreement with a Third Party that requires the payment of any royalty or other financial obligations with respect to sales of Product;

9.1.5 **Compliance with Laws.** In carrying out its work under this Agreement, all Lilly work will be carried out in compliance with any applicable laws including, without limitation, federal, state, or local laws, regulations, or guidelines governing the work at the site where such work

is being conducted. Moreover, Lilly will carry out all work under this Agreement in accordance with current Good Laboratory Practices, Good Clinical Practices, and Good Manufacturing Practices, if applicable based on the specific work to be conducted;

9.1.6 **No Debarment.** Lilly will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Isis that none of its employees nor any person who developed the Product on Lilly's behalf have been debarred under the provisions of such Act;

9.1.7 **Lilly Patents**. To the best of Lilly' knowledge, Lilly does not control any Patent (other than the Lilly Product Patents) that would be infringed by making, using or selling the Product in any country.

9.1.8 **No Warranty of Validity or Non-Infringement**. Notwithstanding any provision of this Agreement to the contrary, Lilly makes no representation or warranty that any of the Lilly Product Patents is valid or that development or sale of the Product would not infringe the rights of any other person.

9.2 **Isis Representations and Warranties.** Isis represents and warrants to Lilly as follows:

9.2.1 **Corporate Existence and Authority.** As of the Effective Date, Isis: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated; (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement; (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder; (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder; and (e) has delivered an Agreement that has been duly executed and constitutes a legal, valid, binding obligation of Isis and is enforceable against it in accordance with its terms;

9.2.2 **Employee Obligations**. All Isis personnel who will conduct research under this Agreement have legal obligations requiring assignment to Isis of all inventions made in the course of and as a result of their association with Isis and obligating the individual to maintain as confidential the confidential information of Isis, as well as the confidential information of Lilly which Isis may receive;

9.2.3 **Compliance with Laws**. In carrying out its work under this Agreement, all Isis work will be carried out in compliance with any applicable laws including, without limitation, federal, state, or local laws, regulations, or guidelines governing the work at the site where such work is being conducted. Moreover, Isis will develop and commercialize the Product under this Agreement in accordance with current Good Laboratory Practices, Good

Clinical Practices, Good Manufacturing Practices, if applicable based on the specific work to be conducted;

9.2.4 **No Debarment.** Isis will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Lilly that none of its employees nor any person providing services to Isis in connection with the development or commercialization of the Product have been debarred under the provisions of such Act; and

9.2.5 **Licenses.** Isis has not taken nor will it take any action which would, in Isis's good faith judgment, interfere with any obligations of Isis set forth in this Agreement, including but not limited to the obligation to grant Lilly the licenses and options described in ARTICLEs 5 and 6.

9.3 **Disclaimer.** EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR WARRANTY TO THE OTHER PARTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING, WITHOUT LIMITATION, ANY WARRANTY OF NON-INFRINGEMENT, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Without limiting the generality of the foregoing, each Party expressly does not warrant (a) the success of any Product; or (b) the safety for any purpose of the technology it provides hereunder.

9.4 **Responsibility and Control.** Lilly and Isis will each be solely responsible for the safety of their respective employees, agents, licensees or (sub)licensees with respect to efforts employed under this Agreement and each will hold the other harmless with regard to any liability for damages or personal injuries resulting from acts of its respective employees, agents, or (sub)licensees in accordance with the indemnification provision set forth in Sections 9.5 through 9.7.

9.5 **Lilly' Right to Indemnification.** Isis will indemnify each of Lilly, its Affiliates, permitted successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Lilly Indemnitees"***), and defend and hold each Lilly Indemnitee harmless from and against any and all liabilities, damages, losses, settlements, claims, actions, suits, penalties, fines, costs or expenses (including, without limitation reasonable attorneys' fees) (any of the foregoing, ***"Damages"***) incurred by or asserted against any Lilly Indemnitee of whatever kind or nature, including, without limitation, any claim or liability based upon negligence, warranty, strict liability, or violation of government regulation but only to the extent arising from or occurring as a result of a claim or demand made by a Third Party (a ***"Third Party Claim"***) against any Lilly Indemnitee arising because of: (a) breach of any representation or warranty made by Isis pursuant to this ARTICLE 9; (b) any material breach of this Agreement by Isis; (c) the manufacture, use, handling, storage, sale or other disposition of the Product that is sold or provided by Isis, its Affiliates, agents or Licensee; and/or (d) violation of the trade secrets of any Third Party by Isis; *except*, in each such case in subparagraphs (a) through (d) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of an Lilly Indemnitee, or the breach of any representation or warranty under Section 9.1 by Lilly.

9.6 **Isis's Right to Indemnification.** Lilly will indemnify each of Isis, its Affiliates, Licensees, successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Isis Indemnitees"***), and defend and hold each Isis Indemnitee harmless from and against any and all Damages incurred by or asserted against any Isis Indemnitee of whatever kind or nature, including, without limitation, any claim or liability based upon negligence, warranty, strict liability, violation of government regulation but only to the extent arising from or occurring as a result of a Third Party Claim against any Isis Indemnitee arising because of: (a) breach of any representation or warranty made by Lilly pursuant to this Article 9; (b) any material breach of this Agreement by Lilly; and/or (c) violation of the trade secrets of any Third Party by Lilly; except, in each such case, in subparagraphs (a) through (c) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of a Isis Indemnitee, or the breach of any representation or warranty under Section 9.2 by Isis.

9.7 **Indemnification Procedures.** Promptly after a Party entitled to indemnification under Section 9.5 or 9.6 (an ***"Indemnitee"***) receives notice of any pending or threatened claim against it (an ***"Action"***), such Indemnitee will give written notice to the Party to whom the Indemnitee is entitled to look for indemnification pursuant to Section 9.5 or 9.6, as applicable (the ***"Indemnifying Party"***), of the commencement thereof, *provided* that the failure so to notify the Indemnifying Party will not relieve it of any liability that it may have to any Indemnitee hereunder, except to the extent the Indemnifying Party demonstrates that it is prejudiced thereby. In case any Action that is subject to indemnification under this ARTICLE 9, will be brought against an Indemnitee and it will give written notice to the Indemnifying Party of the commencement thereof, the Indemnifying Party will be entitled to participate therein and, if it so desires, to assume the defense thereof with counsel reasonably satisfactory to such Indemnitee and, after notice from the Indemnifying Party to the Indemnitee of its election to assume the defense thereof, the Indemnifying Party will not be liable to such Indemnitee under this ARTICLE 9 for any fees of other counsel or any other expenses, in each case subsequently incurred by such Indemnitee in connection with the defense thereof, other than reasonable costs of investigation. Notwithstanding an Indemnifying Party's election to assume the defense of any such Action that is subject to indemnification under this ARTICLE 9, the Indemnitee will have the right to employ separate counsel and to participate in the defense of such Action, and the Indemnifying Party will bear the reasonable fees, costs and expenses of such separate counsel if: (i) the use of counsel chosen by the Indemnifying Party to represent the Indemnitee would present such counsel with a conflict of interest; or (ii) the actual or potential defendants in, or targets of, any such Action include both the Indemnifying Party and the Indemnitee, and the Indemnitee will have reasonably concluded that there may be legal defenses available to it which are different from or additional to those available to the Indemnifying Party (in which case the Indemnifying Party will not have the right to assume the defense of such Action on the Indemnitee's behalf); or (iii) the Indemnifying Party will not have employed counsel satisfactory to the Indemnitee to represent the Indemnitee within a reasonable time after notice of the institution of such Action; or (iv) the Indemnifying Party will authorize the Indemnitee to employ separate counsel at the Indemnifying Party's expense. If an Indemnifying Party assumes the defense of such Action, no compromise or settlement thereof may be effected by the Indemnifying Party without the Indemnitee's written consent, which consent will not be unreasonably withheld or delayed, unless (1) there

is no finding or admission of any violation of law or any violation of the rights of any other Party and no effect on any other claims that may be made against the Indemnitee and (2) the sole relief provided is monetary damages that are paid in full by the Indemnifying Party.

ARTICLE 10

INTELLECTUAL PROPERTY

10.1 **Patent Filing and Prosecution**. Isis (at its own expense) will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Product Patents. Isis will keep Lilly continuously informed of all significant matters relating to the preparation, filing, prosecution and maintenance of the Product Patents. In the event Isis proposes to abandon the prosecution or maintenance of any Product Patent, it shall notify Lilly at least [***] days in advance and allow Lilly to assume the prosecution and maintenance of such patent at Lilly's expense.

10.2 **Patent Term Extensions.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to any Product. The Party selling such Product will determine which patents will be extended. All filings for such extension will be made by the Party to whom the patent is assigned; *provided, however,* that in the event that the Party to whom the patent is assigned elects not to file for an extension, such Party will (i) inform the other Party of its intention not to file; (ii) grant the other Party the right to file for such extension; and (iii) cooperate as necessary to assist the other Party in filing such extension.

10.3 **Notice of Certification.** Isis and Lilly each will immediately upon receiving notice give notice to the other of any certification filed under the U.S. "Drug Price Competition and Patent Term Restoration Act of 1984" claiming that (a) Product Patent Covering the Product, is invalid or that any infringement will not arise from the manufacture, use, sale, offer for sale or import of any product by a Third Party.

10.4 **Notice of Infringement Claim.** If the development or commercialization of a Product under this Agreement results in a claim against a Party for patent infringement or for inducing or contributing to patent infringement (***"Infringement Claim"***), the Party first having notice of an Infringement Claim will promptly notify the other in writing. The notice will set forth the facts of the Infringement Claim in reasonable detail.

10.5 **Responsibilities.** Isis will have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Isis' activities at its own expense and by counsel of its own choice, and Lilly will have the right, at its own expense, to be represented in any such action by counsel of its own choice. Lilly will have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Lilly's activities at its own expense and by counsel of its own choice, and Isis will have the right, at its own expense, to be represented in any such action by counsel of its own choice. Notwithstanding the foregoing, if the claim involves an allegation of a violation of the trade secret rights of a Third Party, the Party accused of such

violation will have the obligation to defend against such claim and will indemnify the other Party against all costs associated with such claim in accordance with Sections 9.5 through 9.7, as applicable. Lilly will not settle any patent infringement litigation under this Section 10.5 relating to any Product Patents without Isis' consent. Isis will not settle any patent infringement litigation under this Section 10.5 relating to any Product Patents without Lilly's consent, if such settlement would materially impair the rights granted to Lilly under Section 5.1, or would impose an obligation on Lilly. Each Party will also keep the other Party continually informed of all significant matters relating to Infringement Claims of Third Parties.

10.6 **Infringement Claims Against Third Parties.**

10.6.1 **Notice of Infringement.** If any Product Patent is infringed or misappropriated, as the case may be, by a Third Party, the Party to this Agreement first having knowledge of such infringement or misappropriation, will promptly notify the other in writing. The notice will set forth the facts of such infringement or misappropriation in reasonable detail. Isis will have the primary right, but not the obligation, to institute, prosecute, and control any action or proceeding with respect to infringement or misappropriation of such Product Patent by its own counsel. Lilly will have the right, at its own expense, to be represented in such action by its own counsel. Except as otherwise agreed to by the Parties in writing as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of any litigation expenses of Lilly and Isis, will be retained by Isis, except that any recovery realized by Isis as a result of such litigation, after reimbursement of the Parties' litigation expenses, will, to the extent attributable to [***] or be treated as [***] of Products by Isis.

10.6.2 **Expenses of Bringing Infringement Action.** Isis will bear the costs and expenses of all infringement or misappropriation actions asserted against a Third Party on Product Patents.

ARTICLE 11

TERM AND TERMINATION

11.1 **Term of Agreement.** This Agreement will commence on the Effective Date and will continue until no payments are due or are capable of becoming due hereunder, unless the Agreement is terminated earlier. All licenses granted hereunder that are in effect at expiration of this Agreement will be deemed fully paid-up and perpetual, except as provided otherwise by this Agreement.

11.2 **Termination for Breach.** Either Party may terminate this Agreement by notice to the other Party at any time during the term of this Agreement if the other Party is in breach of any material obligations hereunder and has not cured such breach within [***] days after notice requesting cure of the breach or such longer period of time as is required to cure such breach as long as the breaching Party is proceeding in good faith to cure; *provided, however,* that in any case when a breach is alleged regarding the payment of money hereunder, the time period will be [***] days and undisputed amounts must be paid prior to

such time to avoid breach. Upon material breach by a Party of its obligations hereunder, if the non-breaching Party decides not to terminate this Agreement, such Party will have the right to [***] any [***] it may incur as a result of curing such breach [***] the amounts [***] to the [***] for the performance of [***]. Further, to the extent that a Party prevails in a lawsuit brought against the other Party for material breach of this Agreement, such prevailing Party will be entitled to collect from the other Party reasonable attorneys' fees and legal costs incurred in connection with such law suit. If the non-breaching Party terminates this Agreement under Section 11.2 following material breach by the breaching Party, the breaching Party will return to the non-breaching Party all of the non-breaching Party's Confidential Information and all materials received from the non-breaching Party during the Agreement, and the breaching Party will cease all use of the non-breaching Party's Confidential Information and materials received from the non-breaching Party for any purpose except as provided in Sections 11.6, and except that the breaching Party may (1) keep a copy of all documents for record keeping purposes only and (2) keep and use any Confidential Information and materials received from the non-breaching Party that are necessary for the breaching Party to exercise those of its rights and fulfill those of its obligations that survive the termination of this Agreement.

11.3 **Termination Upon Insolvency.** Either Party may terminate this Agreement upon notice to the other should the other Party become insolvent or file or consent to the filing of a petition under any bankruptcy or insolvency law or have any such petition filed against it which has not been stayed within sixty (60) days of such filing. During the term of this Agreement, all rights and options or licenses granted under or pursuant to this Agreement by Isis or Lilly are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that, during the term of this Agreement, the Parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either Party under the U.S. Bankruptcy Code, the Party hereto that is not a party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement; or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon written request therefor by the non-subject Party.

11.4 **Effect of Termination Due to Isis Breach or Insolvency.** If Lilly terminates the Agreement based on material breach by or insolvency of Isis, then:

11.4.1 Solely in the event Isis materially breaches its obligation under [***] (or termination by Lilly under Section 11.3 before Isis has met its obligation under [***]), the option granted by Isis to Lilly pursuant to ARTICLE 5 prior to such termination, will survive, but the [***] and the amount of each [***] that would otherwise be payable under

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the Form License Agreement upon exercise of the option shall be reduced by [***] percent ([***]%);

11.4.2 Isis's payment obligations set forth in ARTICLE 7 will continue; *provided, however,* that the amounts of the payments will be increased to reflect the nature of Isis's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which will be borne by Isis;

11.4.3 Any license granted by Isis to Third Party under the Product Patent Rights will continue in full force and effect but the right to collect and receive the royalties under ARTICLE 7 will be assigned by Isis to Lilly, and Isis will provide Lilly with complete and accurate copies of the relevant portions of the license agreement within thirty (30) days following the effective date of such termination;

11.5 **Effect of Termination Due to Lilly Breach or Insolvency.** If Isis terminates the Agreement based on material breach by or insolvency of Lilly, then:

11.5.1 The assignment and technology transfer granted by Lilly to Isis pursuant to Sections 2.2 and 2.3 will survive;

11.5.2 Lilly's option and Right of First Negotiation granted by Isis pursuant to ARTICLE 5 and 6 will terminate;

11.5.3 Isis' payment obligations set forth in ARTICLE 7 will continue, *provided, however,* that the amounts of the payments will be decreased to reflect the nature of Lilly's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which will be borne by Lilly;

11.6 **Accrued Rights/Surviving Obligations.** Except as expressly provided in this Agreement, expiration or termination of this Agreement will not relieve the Parties of any obligation that accrued prior to such expiration or termination, and Isis will be obligated to pay and will pay to Lilly, within [***] days of such expiration or termination, all payments and royalties due or accrued pursuant to the terms of ARTICLE 7. Upon expiration or early termination of this Agreement, all rights and obligations of the Parties will cease, except as follows:

11.6.1 The obligations to pay royalties and other sums accruing hereunder up to the date of termination or expiration will survive;

11.6.2 The obligations of confidentiality set forth in ARTICLE 8 will survive any expiration or termination of this Agreement for a period of five (5) years;

11.6.3 The obligations for record keeping and accounting reports set forth in ARTICLE 7 will survive for so long as Products are sold. At such time after termination or expiration of this Agreement when sales or other dispositions of Products have ceased, Isis will render a final report along with any royalty payment due;

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11.6.4 The termination under Section 2.1 will survive any termination or expiration of the Agreement;

11.6.5 Lilly and Isis' rights to inspect books and records as described in ARTICLE 7 will survive;

11.6.6 The obligations of defense and indemnity set forth in ARTICLE 9 will survive;

11.6.7 Any cause of action or claim of Lilly or Isis accrued or to accrue because of any breach or default by the other Party hereunder will survive; and

11.6.8 All other terms, provisions, representations, rights and obligations contained in this Agreement that are intended to survive as specifically set forth elsewhere in this Agreement will survive.

11.7 **Limitation of Liability.** No Party will be liable to another for indirect, incidental, consequential or special damages, including but not limited to lost profits, arising from or relating to any breach of this Agreement, regardless of any notice of the possibility of such damages. Nothing in this Section is intended to limit or restrict the indemnification rights or obligations of any Party under ARTICLE 9.

ARTICLE 12

PUBLICITY

12.1 **Press Release.** Upon execution of this Agreement, the Parties shall issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties.

12.2 **Disclosure of Agreement.** Neither Party to this Agreement may release any information to any Third Party regarding the terms or existence of this Agreement or the reasons for any termination hereof, without the prior written consent of the other Party. Without limitation, this prohibition applies to press releases, educational and scientific conferences, quarterly investor updates, promotional materials, governmental filings and discussions with public officials, the media, security analysts and investors. However, this provision does not apply to any disclosures regarding this

Agreement or related information to regulatory agencies such as the FDA or Federal Trade Commission and/or Department of Justice for such disclosures which may be required by law, including requests for a copy of this Agreement or related information by tax authorities. If any Party to this Agreement determines a release of information regarding the existence or terms of this Agreement is required by law (including releases a may be required to be filed through the Securities Exchange Commission or other government agency), that Party will notify the other Party as soon as practicable and give as much detail as possible in relation to the disclosure required. The Parties will then cooperate with respect to determining what information should actually be released. The Parties hereby agree that release of a press release upon complete execution of this Agreement is appropriate and such press release will be mutually agreed upon by the Parties.

12.3 **Use of Names, Logos or Symbols.** No Party hereto will use the name, trademarks, logos, physical likeness, employee names or owner symbol of any other Party for any purpose, including, without limitation, private or public securities placements, without the prior written consent of the affected Party, such consent not to be unreasonably withheld or delayed so long as such use of name is limited to objective statements of fact, rather than for endorsement purposes. Nothing contained herein will be construed as granting either Party any rights or license to use any of the other Party's trademarks or tradenames without separate, express written permission of the owner of such trademark or tradename.

12.4 **Publication.** Lilly shall have the right to publish the results of the Ongoing Phase I Study; *provided*, Lilly will coordinate such publication with Isis, including giving Isis at least 5 Business Days in advance of such proposed public disclosure to review and comment on such publication. Isis may publish, present or otherwise disclose results regarding the Product to the public at its sole discretion; *provided, however,* so long as Lilly's option under ARTICLE 5 has not expired or terminated, Isis will share with Lilly any press release or other similar public communication made by Isis that is related to a Product's efficacy or safety data and/or results at least 5 Business Days in advance of such proposed public disclosure. Unless Lilly exercises its option under ARTICLE 5, Lilly will not publicly present or otherwise disclose results regarding the Product without obtaining Isis' prior written consent, such consent not to be unreasonably withheld.

ARTICLE 13

MISCELLANEOUS

13.1 **Force Majeure.** No Party will be held liable or responsible to the other Party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement (except payment obligations) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party including, but not limited to, fire, flood, earthquake, embargo, war, acts of war or terrorism (whether war be declared or not), insurrection, riot, civil commotion, strike, lockout or other labor disturbance, act of God or act, omission or delay in acting by any governmental authority or the other Party. The affected Party will notify the other Party of such force majeure circumstances as soon as reasonably practical.

13.2 **Assignment.** This Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred, by a Party without the written consent of the other Party; *provided, however,* that either Party may, without such consent, assign the Agreement and its rights and obligations hereunder to (i) any wholly-owned subsidiary in a manner such that the assignor (if it continues as a separate entity) will remain liable and responsible for the performance and observance of all its duties and obligations hereunder; and (ii) to any successor by merger or sale of substantially all of its business unit to which this Agreement relates, or in the event of its merger or consolidation or change in control or similar transaction. Lilly may also assign or transfer its rights to receive fees, royalties and milestones under this Agreement (but no liabilities) without Isis consent, to a Third Party in connection with a payment factoring transaction. This Agreement will be binding upon the permitted successors

and permitted assigns of the Parties. Any assignment not in accordance with this Section 13.2 will be void.

13.3 **Severability.** In the event that any of the provisions contained in this Agreement are held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the Parties. The Parties will replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s), which, insofar as practical, implement the purposes of this Agreement.

13.4 **Notices.** All notices or other communications which are required or permitted hereunder will be in writing and deemed to be effective (a) on the date of delivery if delivered in person and written confirmation of delivery is provided; or (b) on the date sent by facsimile or other electronic transmission, provided such receipt is verified; or (c) on the day following date of deposit with an overnight courier if a receipt confirming delivery by overnight courier is provided; or (d) three days after mailing if mailed by first-class certified mail, postage paid, to the respective addresses given below, or to another address as it will designate by written notice given to the other Party.

if to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Operating Officer

with a copy to:

Attention: General Counsel

if to Lilly, to:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Attention: Group Vice President, Lilly Research Laboratories

with a copy to:

Attention: General Patent Counsel

13.5 **Dispute Resolution.** In the event of any controversy or claim arising from or relating to any provision of this Agreement, or any term or condition hereof, or the performance by a Party of its obligations hereunder, or its construction or its actual or alleged breach, the Parties will try to settle their differences amicably between themselves.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

13.6 **Choice of Law.** This Agreement will be governed by and construed in accordance with the laws of the State of New York and the United States without reference to any rules of conflict of laws.

13.7 **Entire Agreement.** This Agreement (including all Schedules hereto), constitute the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangement with respect to the subject matter hereof, whether written or oral. Any amendment or modification to this Agreement will be made in writing signed by both Parties.

13.8 **Headings.** The captions to the several Articles and Sections hereof are not a part of the Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

13.9 **Independent Contractors.** It is expressly agreed that the Parties will be independent contractors and that the relationship between the Parties will not constitute a partnership, joint venture or agency. No Party will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other Parties, without the prior consent of such other Parties.

13.10 **Further Actions.** Each Party agrees to execute, acknowledge and deliver such further instruments, and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of the Agreement.

13.11 **Waiver.** The waiver by a Party hereto of any right hereunder or the failure to perform or of a breach by another Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

13.12 **Jointly Prepared.** This Agreement has been prepared jointly and will not be strictly construed against either Party.

13.13 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

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CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the Effective Date.

ELI LILLY AND COMPANY

By: /s/ Steven Paul
Dr. Steven Paul
Executive Vice President
LRL

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
B. Lynne Parshall
Chief Operating Officer and
Chief Financial Officer

[SIGNATURE PAGE TO DEVELOPMENT AND LICENSE AGREEMENT]

List of Schedules

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

SCHEDULE 1.1

DEFINITIONS

"Affiliate" means any person, organization, corporation or other business entity that controls, directly or indirectly, the power to direct, or cause the direction of, the management and policies of another person, organization, corporation or entity, whether through the ownership of voting securities or by contract or court order or otherwise. For purposes of this definition, an entity will be deemed to control another entity if it owns or controls, directly or indirectly, at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors or their equivalent of such other entity. Regulus Therapeutics Inc., will not be considered an Affiliate of Isis.

"ASO Compound" means an [***].

"Calendar Quarter" will mean the respective three month periods ending on March 31, June 30, September 30, or December 31 for so long as the Agreement is in effect.

"Calendar Year" will mean each successive twelve month period commencing on January 1 and ending on December 31 for so long as the Agreement is in effect.

"cGMP" means U.S. current Good Manufacturing Practices regulations.

"Collaboration Agreement" has the meaning set forth in Recital A of this Agreement.

"Confidential Information" means any and all inventions, know-any, and data and will include, without limitation, information relating to research and development plans, experiments, results and plans, compounds, therapeutic leads, candidates and products, clinical and preclinical data, trade secrets and manufacturing, marketing, financial, regulatory, personnel and other business information and plans, all scientific, clinical, regulatory, marketing, financial and commercial information or data, all whether communicated in writing, orally or by any other means, and which is provided by one Party to the other Party in connection with this Agreement. Confidential Information will not include information that:

(a) is known by the receiving Party at the time of its receipt, and not through a prior disclosure by the disclosing Party, as documented by written records; or

(b) is properly in the public domain through no fault of the receiving Party; or

(c) is subsequently disclosed to the receiving Party by a Third Party who may lawfully do so and is not under an obligation of confidentiality to the disclosing Party; or

(d) is developed by the receiving Party independently of Confidential Information received from the other Party, as documented by written records.

"Control" or ***"Controlled"*** means with respect to any intellectual property right, that the Party owns or has a license to such intellectual property right and has the ability to grant access,

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CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

a license, or a sublicense to such intellectual property right to the other Party as provided for in this Agreement without violating an agreement with, or infringing any rights of, a Third Party as of the time the Party would be first required under this Agreement to grant the other Party such access, license or sublicense.

"Cover" (including variations thereof such as ***"Covering"***, ***"Covered"***, and ***"Coverage"***) means that the manufacture, use, import, offer for sale or sale of a Product would infringe a Valid Claim; provided, with respect to a process or manufacturing patent, that such a Valid Claim therein effectively precludes a Third Party from manufacturing, using, importing, offering for sale, or selling such Product. The determination of whether a Product is Covered by a particular Valid Claim will be made on a country-by-country basis. A Valid Claim will be deemed to provide effective preclusion hereunder where (i) there is no competing product being marketed; or (ii) if a product is being marketed by a competitor, it infringes the Valid Claim (including any period in which, and provided that, the Valid Claim is being litigated).

"Effective Date" has the meaning given to it in the preamble of this Agreement.

"eIF-4E" means eukaryotic initiation factor-4E (Entrez Gene ID: 1977).

"eIF-4E Program" means [***] eIF-4E [***] eIF-4E [***] eIF-4E Program.

"FDA" means the United States Food and Drug Administration or any successor agency having the administrative authority to regulate the approval for marketing of new human pharmaceutical or biological therapeutic products in the United States.

"First Commercial Sale" means with respect to any Product the first sale to a Third Party by Isis, its Affiliates or Licensees under the Product Patent. First Commercial Sale will not include transfer of reasonable quantities of any free samples of a Product or reasonable quantities of Product solely for development purposes, such as for use in experimental studies or clinical trials.

"[***]" means (1) the [***] of the Lilly API by Lilly's [***], including but not limited to (i) a [***] containing the [***] for each lot of Lilly API, and [***] that each such lot of Lilly API [***] to the applicable [***] set forth in the [***] of the [***] for the Product; (ii) a [***] of [***] that the Lilly API was made [***] and the process defined in the [***] for the Lilly API; and (iii) copies of documents detailing any [***] from any [***] then in effect, in each case such documents to be delivered to Isis' VP, Development Chemistry and Manufacturing; and (2) shipment of the Lilly API to Isis' VP, Development Chemistry and Manufacturing in accordance with applicable product specifications for the Lilly API.

"IND" means an Investigational New Drug application as defined in 21 C.F.R. 312 and any versions thereof governing the FDA as may be amended from time to time.

"Initiate" means with respect to a clinical study, the dosing of the first patient in such study.

"Institutional Review Board" means an Institutional Review Board as defined in 21 C.F.R. 56 as may be amended from time to time, or its applicable foreign equivalent.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

"Isis Product Patents" means the Patent Rights listed on Schedule C, and all Patent Rights issuing therefrom.

"Know-How" means all tangible or intangible know-how, inventions (whether patentable or not), discoveries, processes, formulas, data, clinical and preclinical results, non-patented inventions, trade secrets, and any physical, chemical, or biological material or any replication of any such material in whole or in part.

"Licensee" means a Third Party to which Isis has granted a license under the Product Patents to develop and commercialize the Product.

"Lilly Product Patents" means the Patent Rights listed on Schedule B, and all Patent Rights issuing therefrom.

"Lilly Right of First Negotiation" has the meaning set forth in Section 6.2.

"Major Market Country" means the United States, Japan, Germany, the United Kingdom, France, Spain or Italy.

"NDA" means a new drug application or other application filed with the FDA to obtain approval for marketing a Product in the United States, or any future equivalent process.

"Net Sales" means, with respect to a Product, the gross amount invoiced by a Party, its Affiliates or Licensees thereof to unrelated Third Parties, excluding any Licensee, for the Product, less:

(a) Trade, quantity and cash discounts allowed;

(b) Commissions, discounts, refunds, rebates, chargebacks, retroactive price adjustments, and any other allowances which effectively reduce the net selling price;

(c) Product returns and allowances;

(d) That portion of the value associated with the cost of the drug delivery systems;

(e) Any tax imposed on the production, sale, delivery or use of the Product, including, without limitation, sales, use, excise or value added taxes;

(f) Allowance for distribution expenses; and

(g) Any other similar and customary deductions.

Net Sales will be calculated in U.S. Dollars. Such amounts will be determined from the books and records of a Party, its Affiliate or Licensee, maintained in accordance with U.S. Generally Accepted Accounting Principles or, in the case of Licensees, such similar accounting principles, consistently applied. Each Party further agrees in determining such amounts, it will use its then current standard procedures and methodology, including its then current standard

exchange rate methodology for the translation of foreign currency sales into U.S. Dollars or, in the case of Licensees, such similar methodology, consistently applied.

Net Sales excludes:

(i) The transfer of reasonable and customary quantities of free samples of Product(s) and the transfer of Product(s) as clinical trial materials, other than for subsequent resale;

(ii) Sales or transfers of Product(s) among a Party and its Affiliates unless the receiving Party is the consumer or user of the Product(s); and

(ii) Use by a Party or its Affiliates or Licensees of Product for any use connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary marketing approvals for Product (unless such Product is subsequently sold).

In the event that the Product(s) is sold as part of a Combination Product (where ***"Combination Product"*** means any pharmaceutical product which comprises the Product(s) and at least one other active compound(s) and/or ingredients), the Net Sales of the Product(s), for the purposes of determining royalty payments, will be determined by multiplying the Net Sales of Combination Product (as defined in the standard Net Sales definition) by the fraction, A / (A+B) where A is the weighted average sale price of the Product(s) when sold separately in finished form, and B is the weighted average sale price of the other product(s) sold separately in finished form.

In the event that the weighted average sale price of the Product(s) can be determined but the weighted average sale price of the other product(s) cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the fraction A / C where A is the weighted average sale price of the Product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of the other product(s) can be determined but the weighted average sale price of the Product cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the following formula: one (1) minus B / C where B is the weighted average sale price of the other product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of both the Product(s) and the other product(s) in the Combination Product cannot be determined, the Parties will attempt to agree on an appropriate weighted average sale price of both the Product(s) and the other product(s) in the Combination Product, and lacking such agreement the Net Sales of the Product(s) will be deemed to be equal to fifty percent (50%) of the Net Sales of the Combination Product.

The weighted average sale price for a Product, other product(s), or Combination Product will be calculated once each Calendar Year and such price will be used during all applicable royalty reporting periods for the entire Calendar Year. When determining the weighted average sale price of a Product, other product(s), or Combination Product, the weighted average sale price will be calculated by dividing the sales dollars (translated into U.S. Dollars) by the units of active ingredient sold during the twelve (12) months (or the number of months sold in a partial

Calendar Year) for the respective Product(s), other product(s), or Combination Product. In the initial Calendar Year, a forecasted weighted average sale price will be used for Product(s), other product(s), or Combination Product. Any over or under payment due to a difference between forecasted and actual weighted average sale prices will be paid or credited in the first royalty payment of the following Calendar Year.

"Ongoing Phase I Study" means the Lilly Phase I clinical study of the Product, which study is identified internally by the code [***].

"Patent Rights" means: (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; (d) any reissues, substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecutions, continuations-in-part, or divisions of or to any of the foregoing; and (e) term extension or other governmental action which provide exclusive rights beyond the original patent expiration date.

"Phase II Study" means a human clinical trial conducted on a series of patients with the same type of cancer, in each case where the protocol for such phase II study was approved by the applicable Institutional Review Board.

"Phase II Study Initiation" means the dosing of the first patient in the first human clinical trial conducted on a series of patients with the same type and stage of cancer.

"Phase III Study Initiation" means the dosing of the first patient in the first human clinical trial conducted in patients and designed to establish Product safety and efficacy and required to obtain clinical registration of a product with health regulatory authorities such as the FDA.

"Product" means (i) the compound known as LY2275796; and (ii) any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains LY2275796.

"Product Patents" means the Isis Product Patents and the Lilly Product Patents.

"Registration" means (a) in the United States, approval by the FDA of an NDA, or similar application for marketing approval, and satisfaction of any related applicable FDA registration and notification requirements (if any); and (b) in any Major Market Country other than the United States, approval by regulatory authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA and satisfaction of any related applicable regulatory and notification requirements, if any, together with any other approval necessary to make and sell pharmaceuticals and medical devices commercially in such country.

"Registration Submission" means (a) in the United States, acceptance by the FDA of the filing of an NDA, or similar application for marketing approval, for the Product, and (b) in any Major Market Country other than the United States, the filing with the applicable Regulatory

Authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA for the Product.

"Regulatory Authority" means any applicable government entities regulating or otherwise exercising authority with respect to the development and commercialization of the Product.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all regulatory approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all clinical studies and tests, including the manufacturing batch records, relating to the Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files.

"Territory" means the entire world.

"Third Party" means any Party other than Isis or Lilly and their respective Affiliates.

"Valid Claim" means any claim in an issued and unexpired patent which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction following exhaustion of all possible appeal processes and which has not been admitted to be invalid or unenforceable through reissue, reexamination or disclaimer, or otherwise.

Schedule A

Form of License Agreement

Schedule B

Lilly Product Patents as of the Effective Date

[***]

Schedule C

Isis Product Patents as of the Effective Date

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

Schedule D

Form of Patent Assignment

WHEREAS, Eli Lilly and Company ("Assignor"), a Indiana corporation with an address of Lilly Corporate Center, Indianapolis, IN 46285, is the owner of all rights, title, and interests in and to the patents and patent applications shown on the attached Exhibit 1 (the "Patents"); and

WHEREAS, Isis Pharmaceuticals, Inc. ("Assignee"), a Delaware corporation with an address of 1896 Rutherford Road, Carlsbad, California 92008, desires to acquire the entire right, title, and interest in and to the Patents and all the inventions and discoveries disclosed in the Patents (the "Inventions");

NOW THEREFORE, be it known that effective as of [ ], 2009, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Assignor hereby sells, assigns, transfers, and sets over unto Assignee (1) the entire right, title, and interest in all countries throughout the world in and to said Patents and Inventions, including any renewals, revivals, reissues, reexaminations, extensions, continuations, continuations-in-part, and divisions of said Patents and any substitute applications therefor; (2) the entire right to file patent applications ("New Applications") in the name of Assignee or its designee, or in the name of Assignor at Assignee's or its designee's election, on the aforesaid Inventions in all countries of the world; (3) the entire right, title, and interest in and to any patent which issued and may issue on the Inventions in any country, and any renewals, revivals, reissues, reexaminations, and extensions thereof, and any patents of confirmation, registration, and importation of the same; (4) the right to sue and recover for, and the right to profits or damages due or accrued in connection with, any and all past, present, or future infringements of the Patents and Inventions; and (5) the entire right, title, and interest in all convention and treaty rights of all kinds, including without limitation all rights of priority in any country of the world, in and to the above Patents and Inventions;

AND, Assignor hereby authorizes and requests the competent authorities to grant and to issue any and all patents on the Inventions throughout the world to Assignee, its successors, or assigns, whose rights, title, and interests in such patents are the same as would have been held and enjoyed by Assignor had this assignment, sale, and transfer not been made.

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CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

Schedule E

[***]

FORM OF LICENSE AGREEMENT UNDER DEVELOPMENT AND LICENSE AGREEMENT DATED DECEMBER 2, 2009

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

DEVELOPMENT AND LICENSE AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

DEVELOPMENT AND LICENSE AGREEMENT

THIS DEVELOPMENT AND LICENSE AGREEMENT (the ***"Agreement"***) executed on (the ***"Effective Date"***), by and between **ELI LILLY AND COMPANY**, a corporation organized and existing under the laws of Indiana and its Affiliates (together ***"Lilly"***), and **ISIS PHARMACEUTICALS, INC.**, a corporation organized and existing under the laws of Delaware, and its affiliates (together ***"Isis"***).

RECITALS

A. Isis and Lilly have collaborated to discover and develop the Product;

B. Lilly has expertise in the research, manufacturing, development, distribution and sale of pharmaceutical products for human and animal use;

C. Isis and Lilly are parties to the Drug Development and License Option Agreement dated December 2, 2009 (the ***"License Option Agreement"***) pursuant to which Isis granted Lilly the option to acquire the Product;

D. On (the ***"Option Exercise Date"***) Lilly exercised its option under the License Option Agreement; and

E. Lilly wishes to obtain, and Isis wishes to grant, an exclusive license to enable Lilly to develop and commercialize the Product on its own.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained in this Agreement, the Parties agree as follows:

ARTICLE 1

DEFINITIONS; OPTION AGREEMENT TERMINATED

1.1 **Definitions.** Capitalized terms used in this Agreement, whether in the singular or plural, have the meanings set forth in Schedule 1.1 which is attached hereto and made part of this Agreement, or as otherwise specifically defined in this Agreement.

1.2 **Termination of Option Agreement.** The License Option Agreement is hereby terminated and replaced by this Agreement in its entirety. For purposes of clarification, such termination and replacement will not negate the effect of Section 2.1 of the License Option Agreement.

ARTICLE 2

PRODUCT DEVELOPMENT AND COMMERCIALIZTION

2.1 **Development and Commercialization.** As soon as practicable after the Effective Date, the parties will mutually agree upon and implement a commercially reasonable transition plan pursuant to which further development and commercialization activities will be transitioned from Isis to Lilly. The transition plan will provide for transfer to Lilly of relevant data and records, ownership of regulatory filings, and transition of Third Party arrangements (e.g., manufacturing, CRO and similar agreements), and a process for sharing class specific safety data related to the Product. Isis will not be entitled to any compensation or reimbursement for the costs of the first [***] hours of its personnel incurred in transitioning activities to Lilly. Lilly will reimburse Isis for its reasonable direct Third Party costs incurred in connection with transition activities. If Isis and Lilly agree that Isis will continue some of the development of the Product, Isis and Lilly will agree upon a plan and budget to reimburse Isis for such development activities. Following transition of activities to Lilly, Lilly will be solely responsible for all development and commercialization of the Product, including toxicology, clinical development (including taking over and becoming the IND sponsor of all clinical trials that are ongoing as of the Effective Date), regulatory, manufacturing and commercialization efforts, except as agreed otherwise by the Parties. Lilly and its Sublicensees will have the sole right and responsibility for the preparation of any regulatory filings required in order to conduct clinical trials on Product in the Territory, together with the preparation of suitable applications for marketing approval in the Territory and will be the owner and party of record of all such regulatory filings. Isis will cooperate with Lilly, at Lilly's expense, as Lilly reasonably requires in preparing such regulatory filings including, without limitation, any and all data contained therein.

ARTICLE 3

PRODUCT LICENSE

3.1 **Grant of License.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an exclusive, royalty-bearing license, including the right to sublicense, under the Isis Technology solely to develop, make, use, import, offer for sale and sell Products in the Territory.

3.2 **Diligence and Reporting.** In order to maintain the license granted to Lilly under Section 3.1 above, Lilly must maintain an Active Program on the Product, and as long as Lilly has an Active Program on the Product Isis will not conduct any research on its own or with a Third Party on eIF-4E or any ASO Compound directed to eIF-4E. In the event that there is a material, uncured breach of the foregoing diligence obligation by Lilly with respect to the Product, Isis may terminate this Agreement for Lilly breach pursuant to Section 8.5. Lilly will provide Isis with annual written reports that include a description of the research, development and commercialization activities by Lilly on the Product. Lilly will provide prompt written

notice to Isis when it ceases to have an Active Program on the Product and thereafter such license will terminate. Within [***] months of such notice from Lilly, or within [***] months of termination of this Agreement by Isis pursuant to this Section 3.2 or Section 8.2, Isis will provide written notice to Lilly if it desires to develop a Product and whether it desires to receive from Lilly summary reports on completed IND-enabling toxicology studies and completed

clinical trials for the Product. Lilly will provide such summary reports promptly after receiving such notice from Isis. If Isis fails to provide such notice within such [***] month period Lilly will have no obligation to provide such summary reports to Isis. For purposes of clarity, if Isis fails to request such summary reports from Lilly for a Product as described above in this Section 3.2, Isis may still develop a Product.

3.3 **No Implied Licenses.** Except as expressly provided otherwise herein, neither Party hereto will be deemed by this Agreement to have been granted any license or other rights to the other Party's intellectual property rights including any Third Party patent rights.

3.4 **Negative Covenant of Isis.** Isis hereby agrees that, for so long as Lilly's exclusive license under Section 3.1 is in effect, Isis will not (a) pursue research, development or commercialization of [***] to eIF-4E outside this Agreement, either on its own or for a Third Party, or (b) grant or assign to any Third Party any rights to [***] to eIF-4E.

ARTICLE 4

PAYMENTS AND ACCOUNTING

4.1 **Payment Tiers.** The license fee and milestones payable by Lilly to Isis under this Agreement will depend upon whether Isis has Initiated certain Phase II Studies for the Product for certain market types by the Option Exercise Date as follows:

4.1.1 If, by the Option Exercise Date, Isis has Initiated either (i) at least [***] Phase II Study of the Product in at least [***], or (ii) [***] or more Phase II Studies of the Product in at least [***], then Lilly will pay Isis the license fee and milestones set forth in this ARTICLE 4 at the ***"Tier 1 Rates"***.

4.1.2 If, by the Option Exercise Date, Isis has Initiated [***] or more Phase II Studies of the Product in only [***], then Lilly will pay Isis the license fee and milestones set forth in this ARTICLE 4 at the ***"Tier 2 Rates"***.

4.1.3 If, by the Option Exercise Date, Isis has only Initiated Phase II Studies of the Product in [***], then Lilly will pay Isis the license fee and milestones set forth in this ARTICLE 4 at the ***"Tier 3 Rates"***.

4.1.4 Lilly will pay Isis a license fee and milestones based on the single highest payment tier set forth in this Section 4.1 that Isis has qualified for with the Product. For purposes of clarification, the payment tiers above will be set regardless of the outcome of any Phase II Study referenced above.

4.2 **License Fees.**

4.2.1 Depending on which payment tier applies as determined under Section 4.1 above, Lilly will pay Isis a one-time, non-refundable, non-creditable fee in accordance with the table below, payable within 30 days following the Effective Date.

	Tier 1 Rates	Tier 2 Rates	Tier 3 Rates
Applicable License Fee:	$ [***]	$ [***]	$ [***]

4.2.2 In addition, if Lilly did not complete the [***] by [***], as set forth in ARTICLE 4 of the License Option Agreement, then Lilly will pay Isis an additional one-time, non-refundable, non-creditable fee of $[***], payable within 60 days following the Effective Date.

4.3 **Milestone Payments.** Depending on which payment tier applies as determined under Section 4.1 above, Lilly will pay to Isis the following milestone payments for a Product within 30 days after the first achievement by Lilly, its Affiliates or Sublicensees of each of the following events in the first Major Market Country:

	Milestone Payment		
Milestone Event	**Tier 1 Rates**	**Tier 2 Rates**	**Tier 3 Rates**
[***]	$ [***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]	$ [***]
[***]	$ [***]	$ [***]	$ [***]
[***]	[***]	$ [***]	$ [***]
[***]	[***]	[***]	$ [***]
Total:	**$ [***]**	**$ [***]**	**$ [***]**

Each milestone payment set forth above is only payable once, even if more than one Product achieves the same milestone.

4.4 **Royalties.** Lilly will pay to Isis the following royalties on a country-by-country basis from the date of the First Commercial Sale of a Product in each such country until the later of (i) the expiration of the last to expire Isis Patent Right that includes a Valid Claim that Covers such Product; and (ii) [***] years from the First Commercial Sale:

Worldwide Annual Net Sales of the Product	**Royalty Rate**
On the portion of Net Sales from US$[***] to less than US$[***]	[***]%
On the portion of Net Sales from US$[***] to less than US$[***]	[***]%
On the portion of Net Sales equal to or more than US$[***]	[***]%

4.5 **Pass Through Royalties.** With respect to Products, Isis will be responsible for paying the pass through royalties or other compensation payable by Isis under (i) the [***], (ii) the [***] and (iii) except as provided under Section 4.6.2, any other agreement executed by Isis under which agreement Isis has agreed to pay a Third Party royalties based upon sales of the Product.

4.6 **Access to Third Party Rights.**

4.6.1 **Third Party Licenses.** If, after the Effective Date access to a Third Party's intellectual property rights becomes necessary to make, use, import, or offer to sell, or sell a Product in the Territory, Lilly will have the right to acquire such access. [***] percent ([***]%) of the acquisition cost paid by Lilly (*i.e.*, all consideration paid by Lilly in connection with such acquisition including, without limitation up-front payments, milestones payments and royalties) applicable to such Product will be credited against future royalties owed to Isis by Lilly under this Agreement for a Product. Except as the Parties may otherwise agree in writing, under no circumstance will Lilly acquisitions of Third Party intellectual property rights under the provisions of this Section 4.5.1 result in a reduction of Net Royalties payable to Isis under this Agreement by more than [***] ([***]%) percent of the royalty otherwise due to Isis.

4.6.2 **Oral Preparation, Formulation or Delivery Technology.** Any oral preparation, formulation or delivery technology that is applicable to the Product that is obtained by Isis from any Affiliate or Third Party, including [***], will be made available to Lilly, at Lilly's discretion, for use at a cost (including royalties, milestones and other payments) that is no greater than the [***] payable by Isis to such Third Party. Any oral preparation, formulation or delivery technology developed by Isis during the term of the Agreement that is applicable to the Products will be made available to Lilly hereunder as Isis Technology.

4.6.3 **Royalty Obligations.** Except as otherwise provided in this Agreement both Parties acknowledge and agree that each is solely responsible for any and all royalty obligations that have accrued or may accrue in the future with respect to any agreements and/or arrangement that such Party may have agreed to prior to the Effective Date. Except as otherwise provided in this Agreement, any Third Party technology acquired by Isis that is applicable to the Product will be made available to Lilly at the cost (including royalties, milestones and other payments) payable by Isis to such Third Party.

4.7 **Compulsory License.** If in any country a Third Party obtains a Compulsory License to sell a Product, then Lilly or Isis, respectively, will promptly notify the other Party. If the royalty rate payable by the grantee of the Compulsory License is less than the then-current royalty rate paid under this Agreement, then the royalty rate, payable under this Agreement with respect to such Product, will be reduced to such lower rate in the subject country for so long as sales are made pursuant to the Compulsory License; *provided*, *however,* that in no event will the Net Royalty to Isis fall below [***] percent ([***]%).

4.8 **Inflation.** The increments of annual Net Sales tiers set forth in Sections 4.3 will be adjusted on a Calendar Year basis commencing January 1, [***] (and on January 1 of each year thereafter during the term of this Agreement) by an amount equal to the percentage change, if any, in the CPI for the preceding year.

4.9 **Accounting Reports; Payment of Royalty.** Lilly (including its Affiliates) and its Sublicensees will keep complete and accurate books and records which may be necessary to ascertain properly and to verify the payments owed hereunder. To the extent Lilly has prepared such information for its own purposes, if requested in writing by Isis, Lilly will provide to Isis [***] ([***]) days after the end of each Calendar Quarter a written report with Lilly's good faith estimate of Lilly's Net Sales accrued in the preceding Calendar Quarter and the royalties payable thereon. Lilly will make royalty payments to Isis for Products sold by Lilly, its Affiliates and Sublicensees during the Calendar Quarter within [***] ([***]) days of the last day of that Calendar Quarter. Each royalty payment will be accompanied by a written report for that Calendar Quarter showing the Net Sales of the Products sold by Lilly, its Affiliates and Sublicensees worldwide during the quarterly reporting period and the calculation of the royalties payable under this Agreement.

4.10 **Audits.** Upon Isis' written request, and not more than once in each Calendar Year, Lilly will permit Lilly's independent certified public accountant to have access during normal business hours to such of Lilly's records as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the current year and the preceding [***] ([***]) years prior to the date of such request. Isis will submit an audit plan, including audit scope, to Lilly for Lilly's approval, which will not be unreasonably withheld, prior to audit implementation. The independent certified public accountants will keep confidential any information obtained during such inspection and will report to Isis only the amounts of Net Sales and royalties due and payable. Upon the expiration of [***] ([***]) years following the end of any Calendar Year, the calculation of royalties payable with respect to such year will be binding and conclusive upon Isis, and Lilly and its Affiliates and Sublicensees will be released from any liability or accountability with respect to royalties for such year. If such accounting firm concludes that additional royalties were owed, or that Lilly overpaid royalties, during such period, Lilly will pay the additional royalties, or Isis will return any overpaid royalties, within [***] ([***]) days of the date Isis delivers to Lilly such accounting firm's written report. The fees charged by such accounting firm will be paid by Lilly unless the additional royalties owed by Lilly exceed [***] percent ([***]%) of the royalties paid for the royalty period subject to the audit, in which case Lilly will pay the reasonable fees of the accounting firm. Lilly will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to make reports to Lilly, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by a mutually agreed upon independent accountant to the

same extent required of Lilly under this Agreement. Lilly will treat all financial information subject to review under this Section 4.10 or under any sublicense agreement in accordance with the confidentiality provisions of this Agreement, and will cause its accounting firm to enter into an acceptable confidentiality agreement with Lilly obligating it to retain all such financial information in confidence pursuant to such confidentiality agreement.

4.11 **Payment.** All payments to Isis under this Agreement will be made in United States Dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by Isis from time to time. Lilly will pay a late payment service charge of [***]% per month (or the highest amount allowed by law, if lower than [***]%) on all past-due amounts owed by such Party under this Agreement.

4.12 **Income Tax Withholding.** Each Party will be responsible for its own tax liabilities resulting from the payments received from the other Party under this Agreement. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this

ARTICLE 4, the paying Party will make such withholding payments as required and subtract such withholding payments from the payments set forth in this ARTICLE 4. The paying Party will submit appropriate proof of payment of the withholding taxes to the other Party within a reasonable period of time.

ARTICLE 5

CONFIDENTIALITY

5.1 **Nondisclosure and Nonuse Obligations.** All Confidential Information disclosed by one Party to the other Party hereunder will be maintained in confidence and will not be disclosed to any Third Party or used for any purpose except as expressly permitted herein without the prior written consent of the other Party.

5.2 **Permitted Disclosure of Confidential Information.** Notwithstanding Section 5, a Party may disclose Confidential Information of the other Party as follows:

5.2.1 to appropriate U.S. and/or foreign tax authorities, appropriate patent agencies in order to obtain Patent Rights pursuant to this Agreement, appropriate regulatory authorities to gain approval to conduct clinical trials or to market Products pursuant to this Agreement, but such disclosure, may be only to the extent reasonably necessary to obtain such Patent Rights or authorizations;

5.2.2 if required by any governmental authority other than under Section 5.2.1, provided that prior to such disclosure, the Party subject to the request for such disclosure (the ***"Notifying Party"***) promptly notifies the other Party of such requirement so that such other Party may seek a protective order or other appropriate remedy; and *provided*, *further*, that in the event that no such protective order or other remedy is obtained, or that such other Party waives compliance with this ARTICLE 5, the Notifying Party will furnish only that portion of the other Party's Confidential Information that it is advised by counsel it is legally required to furnish and will exercise all reasonable efforts to obtain reasonable assurance that confidential treatment will be accorded the other Party's Confidential Information so furnished;

5.2.3 by a Party to its permitted Sublicensees, agents, consultants, Affiliates and/or other Third Parties for the research and development, manufacturing and/or marketing of Products (or for such Parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Affiliates and Third Parties agree to be bound by the confidentiality and non-use obligations contained in this Agreement; or

5.2.4 if required to be disclosed by law or court order, provided that notice is promptly delivered to the non-disclosing Party in order to provide an opportunity to challenge or limit the disclosure obligations.

ARTICLE 6

DISCLAIMERS, REPRESENTATIONS, WARRANTIES AND INDEMNIFICATIONS

6.1 **Isis Representations and Warranties.** Isis represents and warrants to Lilly as follows:

6.1.1 **Corporate Existence and Authority.** As of the Option Exercise Date, Isis: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated, (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement, including the right to grant the options to license and licenses granted hereunder, (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder, and (e) has delivered an Agreement that has been duly executed and constitutes a legal, valid, binding obligation of Isis and is enforceable against it in accordance with its terms;

6.1.2 **Patents, Prior Art.** As of the Option Exercise Date and to the best of Isis' knowledge, it has the sufficient legal and/or beneficial title and ownership under the Isis Technology as is necessary to fulfill its obligations under this Agreement and to grant the licenses and options to license to Lilly pursuant to this Agreement. Isis is not aware of any communications alleging that it has violated or, by conducting its business as currently proposed under this Agreement, would violate any of the intellectual property rights of any Third Party;

6.1.3 **Absence of Litigation, Infringement, Misappropriation**. As of the Option Exercise Date and to the best of Isis' knowledge, there is no pending or threatened litigation (and Isis has not received any communication relating thereto) which alleges that Isis' activities in developing the Product infringe or misappropriate any intellectual property rights of any Third Party. To the best of Isis' knowledge, there is no material unauthorized use, infringement or misappropriation of any of its intellectual property rights that are the subject of the licenses or options to license granted hereunder;

6.1.4 **Upstream Licenses**. True and correct copies of the Upstream Licenses have previously been provided to Lilly by Isis. The Upstream Licenses are in full force and effect as of the Effective Date, and Isis is not in material breach of any of the provisions of any

of the Upstream Licenses, nor does there exist any condition that, to the knowledge of Isis, with passage of time or sending of notice would constitute a material breach by Isis of any of the provisions of the Upstream Licenses, nor is Isis aware of any material breach of the Upstream Licenses by any other party thereto. Isis has not waived any material rights under any Upstream Licenses. Isis will not amend or terminate any Upstream License or waive any rights under any Upstream License during the term of this Agreement without the prior written consent of Lilly. Isis will fulfill all of its material obligations under the Upstream Licenses and otherwise comply with the terms thereof, and, notwithstanding any other provisions of this Agreement to the contrary, will be solely responsible for and pay when due any payments due under the Upstream Licenses. Isis shall exercise its rights under the Upstream Licenses in a manner consistent with the intent and terms of this Agreement.

6.1.5 **Full Disclosures.** Isis has provided Lilly with all information that Lilly has requested for deciding the merits of entering into this Agreement and all information reasonably useful or necessary to enable Lilly to make an informed decision regarding entering into this Agreement;

6.1.6 **Employee Obligations**. All Isis employees who will conduct research under this Agreement have legal obligations requiring assignment to Isis of all inventions made in the course of and as a result of their association with Isis and obligating the individual to maintain as confidential the Confidential Information of Isis, as well as the Confidential Information of Lilly which Isis may receive;

6.1.7 **No Debarment.** Isis will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Lilly that none of its employees nor any person providing services to Isis in connection with this Agreement have been debarred under the provisions of such Act; and

6.1.8 **Licenses**. Isis has not taken nor will it take any action which would, in Isis' good faith judgment, interfere with any obligations of Isis set forth in this Agreement, including but not limited to the licenses granted by Isis to Lilly under ARTICLE 3.

6.2 **Lilly Representations and Warranties.** Lilly represents and warrants to Isis as follows:

6.2.1 **Corporate Existence and Authority.** As of the Effective Date, Lilly: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated, (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement, including the right to grant the options to license and licenses granted hereunder, (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder, and (e) has delivered an Agreement that has been duly

executed and constitutes a legal, valid, binding obligation of Lilly and is enforceable against it in accordance with its terms;

6.2.2 **Employee Obligations**. All Lilly personnel who will conduct research or development under this Agreement have legal obligations requiring assignment to Lilly of all inventions made in the course of and as a result of their association with Lilly and obligating the individual to maintain as confidential the confidential information of Lilly, as well as the confidential information of Isis which Lilly may receive;

6.2.3 **Compliance with Laws**. In carrying out its work under this Agreement, all Lilly work will be carried out in compliance with any applicable laws including, without limitation, federal, state, or local laws, regulations, or guidelines governing the work at the site where such work is being conducted. Moreover, Lilly will carry out all work under this Agreement in accordance with current Good Laboratory Practices, Good Clinical Practices, Good Manufacturing Practices, if applicable based on the specific work to be conducted; and

6.2.4 **No Debarment.** Lilly will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Isis that none of its employees nor any person providing services to Lilly in connection with this Agreement have been debarred under the provisions of such Act.

6.3 **Disclaimer.** EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR WARRANTY TO THE OTHER PARTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING, WITHOUT LIMITATION, ANY WARRANTY OF NON-INFRINGEMENT, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Without limiting the generality of the foregoing, each Party expressly does not warrant (a) the success of any Product or (b) the safety for any purpose of the technology it provides hereunder.

6.4 **Responsibility and Control.** Lilly and Isis will each be solely responsible for the safety of their respective employees, agents, licensees or Sublicensees with respect to efforts employed under this Agreement and each will hold the other harmless with regard to any liability for damages or personal injuries resulting from acts of its respective employees, agents, licensees or Sublicensees.

6.5 **Isis' Right to Indemnification.** Lilly will indemnify each of Isis, its Affiliates, Sublicensees, permitted successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Isis Indemnitees"***), and defend and hold each Isis Indemnitee harmless from and against any and all liabilities, damages, losses, settlements, claims, actions, suits, penalties, fines, costs or expenses (including, without limitation reasonable attorneys' fees) (any of the foregoing, ***"Damages"***) incurred by or asserted against any Isis Indemnitee of whatever kind or nature, including, without limitation, any claim or liability based upon negligence, warranty, strict liability, or violation of government regulation but only to the extent arising from or occurring as a result of a claim or demand made by a Third Party (a ***"Third Party Claim"***) against any Isis Indemnitee arising because of: (a) breach of any representation or warranty made by Lilly pursuant to this ARTICLE 6; (b) any material breach of this Agreement by Lilly; (c) the manufacture, use, handling, storage, sale or other disposition of a Product that is

sold or provided by Lilly, its Affiliates, agents or Sublicensees; and/or (d) violation of the trade secrets of any Third Party by Lilly; except, in each such case in subparagraphs (a) through (d) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of an Isis Indemnitee, or the breach of any representation or warranty under Section 6.1 by Isis.

6.6 **Lilly's Right to Indemnification.** Isis will indemnify each of Lilly, its Affiliates, Sublicensees, successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Lilly Indemnitees"***), and defend and hold each Lilly Indemnitee harmless from and against any and all Damages incurred by or asserted against any Lilly Indemnitee of whatever kind or nature, including, without limitation, any claim or liability based upon negligence, warranty, strict liability, violation of government regulation but only to the extent arising from or occurring as a result of a Third Party Claim against any Lilly Indemnitee arising because of: (a) breach of any representation or warranty made by Isis pursuant to this ARTICLE 6; (b) any material breach of this Agreement by Isis; (c) the manufacture, use, handling, storage, sale or other disposition of a Product that is sold or provided by Isis, its Affiliates, agents or Sublicensees; (d) violation of the trade secrets of any Third Party by Isis and/or (e) any Third Party Claim that any Isis Technology

should not have been disclosed or made available to Lilly; except, in each such case, in subparagraphs (a) through (e) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of a Lilly Indemnitee, or the breach of any representation or warranty under Section 6.2 by Lilly.

6.7 **Indemnification Procedures.** Promptly after a Party entitled to indemnification under Section 6.5 or 6.6 (an ***"Indemnitee"***) receives notice of any pending or threatened claim against it (an ***"Action"***), such Indemnitee will give written notice to the Party to whom the Indemnitee is entitled to look for indemnification pursuant to Section 6.5 or 6.6, as applicable (the ***"Indemnifying Party"***), of the commencement thereof, provided that the failure so to notify the Indemnifying Party will not relieve it of any liability that it may have to any Indemnitee hereunder, except to the extent the Indemnifying Party demonstrates that it is prejudiced thereby. In case any Action that is subject to indemnification under this ARTICLE 6, will be brought against an Indemnitee and it will give written notice to the Indemnifying Party of the commencement thereof, the Indemnifying Party will be entitled to participate therein and, if it so desires, to assume the defense thereof with counsel reasonably satisfactory to such Indemnitee and, after notice from the Indemnifying Party to the Indemnitee of its election to assume the defense thereof, the Indemnifying Party will not be liable to such Indemnitee under this ARTICLE 6 for any fees of other counsel or any other expenses, in each case subsequently incurred by such Indemnitee in connection with the defense thereof, other than reasonable costs of investigation. Notwithstanding an Indemnifying Party's election to assume the defense of any such Action that is subject to indemnification under this ARTICLE 6, the Indemnitee will have the right to employ separate counsel and to participate in the defense of such Action, and the Indemnifying Party will bear the reasonable fees, costs and expenses of such separate counsel if: (i) the use of counsel chosen by the Indemnifying Party to represent the Indemnitee would present such counsel with a conflict of interest; (ii) the actual or potential defendants in, or targets of, any such Action include both the Indemnifying Party and the Indemnitee, and the Indemnitee will have reasonably concluded that there may be legal defenses available to it which are different from or additional to those available to the Indemnifying Party (in which case the

Indemnifying Party will not have the right to assume the defense of such Action on the Indemnitee's behalf); (iii) the Indemnifying Party will not have employed counsel satisfactory to the Indemnitee to represent the Indemnitee within a reasonable time after notice of the institution of such Action; or (iv) the Indemnifying Party will authorize the Indemnitee to employ separate counsel at the Indemnifying Party's expense. If an Indemnifying Party assumes the defense of such Action, no compromise or settlement thereof may be effected by the Indemnifying Party without the Indemnitee's written consent, which consent will not be unreasonably withheld or delayed, unless (1) there is no finding or admission of any violation of law or any violation of the rights of any other Party and no effect on any other claims that may be made against the Indemnitee and (2) the sole relief provided is monetary damages that are paid in full by the Indemnifying Party.

ARTICLE 7

INTELLECTUAL PROPERTY

7.1 **Patent Filing and Prosecution**. Except as provided in Section 7.2, Isis will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Isis Patent Rights.

7.2 Lilly at its own expense, will prepare, file, prosecute and/or maintain the Isis ASO Compound Patent Rights that are exclusively licensed by Lilly pursuant to Section 3.1. In the event of termination under Section 3.2 or 8.5, or upon written agreement of the Parties, such responsibility and expense for preparation, filing, prosecuting and maintenance will revert back to Isis. Lilly may use in-house patent counsel or outside patent counsel that is acceptable to Isis for the filing, prosecution and maintenance of Isis ASO Compound Patent Rights for which Lilly assumes responsibility for under this Section 7.2. Isis will promptly transfer the subject patent files to Lilly and will execute such documents and perform such acts as may be reasonably necessary for Lilly to take control of such patent filing, prosecution and maintenance and will provide all necessary assistance in the prosecution and maintenance thereof. Lilly will, in a timely manner, provide Isis with copies of all draft applications, responses and other substantive papers relating to the filing, prosecution and maintenance (including the verification of all fees and annuities) of such Isis ASO Compound Patent Rights and will provide Isis with an opportunity to comment on any draft applications, responses or amendments at least [***] days prior to filing and to the extent practicable incorporate such comments. Isis hereby acknowledges a possible conflict of interest between Lilly and Isis relating to the Isis ASO Compound Patent Rights for which Lilly assumes responsibility for filing, prosecution and maintenance under this Section 7.2. So long as Lilly complies with provisions of this Section 7.2, Isis hereby grants Lilly and Lilly's patent counsel a conflict waiver, to the limited extent of any conflict of interest arising from the fact that (a) Lilly has the right to prepare, file, prosecute and maintain the Isis ASO Compound Patent Rights pursuant to this Section 7.2 and (b) Isis owns or Controls such Patent Rights. Isis and Lilly will discuss in good faith assignment of any ASO Compound Patent Rights to Lilly.

7.3 **Election Not to File, Prosecute or Maintain.** If Lilly elects to discontinue prosecution or maintenance of any Isis ASO Compound Patent Right for which Lilly assumes responsibility for filing, prosecution and maintenance (or that is assigned to Lilly) under Section

7.2, then Lilly will give [***] days advance written notice to Isis of any decision to cease preparation, filing, prosecution and maintenance of that Patent Right (a ***"Discontinued Patent"***); *provided, however,* that abandonment of a patent application in favor of a continuation or a continuation-in-part thereof will not constitute discontinuance of the patent application. In such case, Isis may elect at its sole discretion to continue preparation, filing, prosecution or maintenance of the Discontinued Patent at its sole expense, and Isis will own any such patent application and patents maturing therefrom and be solely responsible for all costs, and Lilly will have a non-exclusive, worldwide, royalty-bearing (under Section 4.3) license to continue to practice such Discontinued Patent, including the right to sublicense solely to develop, make, use, import, offer for sale and sell a Product, in accordance with the terms of Section 3.1. Lilly will execute such documents and perform such acts as may be reasonably necessary for Isis to file or to continue prosecution or maintenance, including assigning ownership of such patents and inventions to Isis. Discontinuance may be on a country-by-country basis or for a patent application or patent series in total.

7.4 **Costs and Expenses.** Lilly will bear its own costs and expenses in filing, prosecuting, maintaining and extending the Isis ASO Patent Rights. Isis will bear its own costs and expenses in filing, prosecuting, maintaining and extending the Isis Core Technology Patent Rights and the Isis Manufacturing Patent Rights.

7.5 **Patent Term Extensions.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to any Product. The Party selling such Product will determine which patents will be extended. All filings for such extension will be made by the Party selling such Product; *provided, however,* that in the event that the Party to selling such Product elects not to file for an extension, such Party will (i) inform the other Party of its intention not to file, (ii) grant the other Party the right to file for such extension, and (iii) cooperate as necessary to assist the other Party in filing such extension.

7.6 **Notice of Certification.** Isis and Lilly each will immediately upon receiving notice give notice to the other of any certification filed under the U.S. "Drug Price Competition and Patent Term Restoration Act of 1984" claiming that an Isis Patent Right Covering a Product being developed or commercialized by Lilly hereunder is invalid or that any infringement will not arise from the manufacture, use, sale, offer for sale or import of any product by a Third Party. If permitted under Section 7.2 and Lilly decides not to bring infringement proceedings against the entity making such a certification with respect to a Isis Patent Right Covering a Product being developed or commercialized by Lilly hereunder, Lilly will give notice to Isis of its decision not to bring suit within twenty-one (21) days after receipt of notice of such certification. Isis may then, but is not required to, bring suit against the entity that filed the certification. Any suit by Lilly or Isis will either be in the name of Lilly or in the name of Isis, or jointly by Lilly and Isis, as may be required by law. For this purpose, the Party not bringing suit will execute such legal papers necessary for the prosecution of such suit as may be reasonably requested by the Party bringing suit. Any costs incurred or benefits received as a result of proceeding under this Section 7.6 will be paid or received entirely by the Party who pursued the action.

7.7 **Notice of Infringement Claim.** If the practice of a license granted to a Party under this Agreement results in a claim against a Party for patent infringement or for inducing or contributing to patent infringement (***"Infringement Claim"***), the Party first having notice of an

Infringement Claim will promptly notify the other in writing. The notice will set forth the facts of the Infringement Claim in reasonable detail.

7.8 **Responsibilities.** Isis will have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Isis' activities at its own expense and by counsel of its own choice, and Lilly will have the right, at its own expense, to be represented in any such action by counsel of its own choice. Lilly will have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Lilly's activities at its own expense and by counsel of its own choice, and Isis will have the right, at its own expense, to be represented in any such action by counsel of its own choice. Notwithstanding the foregoing, if the claim involves an allegation of a violation of the trade secret rights of a Third Party, the Party accused of such violation will have the obligation to defend against such claim and will indemnify the other Party against all costs associated with such claim (in accordance with Sections 6.5 through 6.7). Neither Party will have the right to settle any patent infringement litigation under this Section 7.8 relating to any Patent Rights owned by or exclusively licensed to the other Party hereunder without the consent of such other Party. Each Party will also keep the other Party continually informed of all significant matters relating to Infringement Claims of Third Parties.

7.9 **Infringement Claims Against Third Parties.**

7.9.1 **Protection Against Infringement.** Isis and Lilly each agree to take reasonable actions to protect their respective patents and technology from infringement and from unauthorized possession or use.

7.9.2 **Notice of Infringement.** If any Isis ASO Compound Patent Right licensed by Isis to Lilly under this Agreement is infringed or misappropriated, as the case may be, by a Third Party, the Party to this Agreement first having knowledge of such infringement or misappropriation, will promptly notify the other in writing. The notice will set forth the facts of such infringement or misappropriation in reasonable detail. In such case, Lilly will have the primary right, but not the obligation, to institute, prosecute, and control any action or proceeding with respect to infringement or misappropriation of such Isis ASO Compound Patent Right by its own counsel. The other Party will have the right, at its own expense, to be represented in such action by its own counsel. Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of any litigation expenses of Isis and Lilly, will be retained by the Party that brought and controlled such litigation for purposes of this Agreement, except that any recovery realized by Lilly as a result of such litigation, after reimbursement of the Parties' litigation expenses, will, to the extent [***] to [***], be treated as [***] of [***] by Lilly.

7.9.3 **Expenses of Bringing Infringement Action.** Subject to Section 7.9.2, Lilly will bear the costs and expenses of all infringement or misappropriation actions brought by Lilly under this Agreement. Subject to Section 7.9.2, Isis will bear the costs and expenses of all infringement or misappropriation actions brought by Isis under this Agreement.

7.9.4 **Lilly's Failure to Institute, Prosecute and Control.** If Lilly fails to institute, prosecute, and control such action or prosecution within a period of [***] days after

receiving notice of the infringement, Isis, subject to the prior rights of any Third Party, will have the right to bring and control any such action by counsel of its own choice, and Lilly will have the right, at its own expense, to be represented in any such action by counsel of its own choice. Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of 100% of any litigation expenses of Isis and 100% of any litigation expenses of Lilly (including the costs and expenses incurred by Lilly in providing reasonable assistance to Isis), will be shared [***] by the Parties. No settlement or consent judgment or other voluntary final disposition of a suit under this Section 7.9.4 may be entered into without the joint consent of Isis and Lilly (which consent will not be unreasonably withheld or delayed).

7.9.5 **Settlement Approval.** Neither Party will settle any such proceeding under this Section 7.9 without the approval of the other Party, which approval will not be unreasonably withheld or delayed.

ARTICLE 8

TERM AND TERMINATION

8.1 **Term of Agreement.** This Agreement will commence on the Effective Date and will continue until no payments are due or are capable of becoming due hereunder, unless the Agreement is terminated earlier in accordance with this ARTICLE 8. All licenses granted hereunder that are in effect at expiration of this Agreement will be deemed fully paid-up and perpetual (as more specifically described in 8.6.1 below), except as provided otherwise by this Agreement.

8.2 **Termination for Breach.** Either Party may terminate this Agreement by notice to the other Party at any time during the term of this Agreement if the other Party is in breach of any material obligations hereunder and has not cured such breach within ninety (90) days after notice requesting cure of the breach or such longer period of time as is required to cure such breach as long as the breaching Party is proceeding in good faith to cure; *provided, however,* that in any case when a breach is alleged regarding the payment of money hereunder, the time period will be thirty (30) days and undisputed amounts must be paid prior to such time to avoid breach. Upon material breach by a Party of its obligations hereunder, if such Party decides not to terminate this Agreement, such Party will have the right to offset any costs it may incur as a result of curing such breach against the amounts payable to the breaching Party for the performance of such obligations. Further, to the extent that a Party prevails in a lawsuit brought against the other Party for material breach of this Agreement, such prevailing Party will be entitled to collect from the other Party reasonable attorneys' fees and legal costs incurred in connection with such law suit. If the non-breaching Party terminates this Agreement under Section 8.2 following material breach by the breaching Party, the breaching Party will return to the non-Breaching Party all of the non-breaching Party's Confidential Information and all materials received from the non-breaching Party during the Agreement, and the breaching Party will cease all use of the non-breaching Party's Confidential Information and materials received from the non-breaching Party for any purpose except as provided in Section 8.7, and except that the breaching Party may (1) keep a copy of all documents for record keeping purposes only and (2) keep and use any Confidential Information and materials received from the non-breaching

Party that are necessary for the breaching Party to exercise those of its rights and fulfill those of its obligations that survive the termination of this Agreement.

8.3 **Termination Upon Insolvency.** Either Party may terminate this Agreement upon notice to the other should the other Party become insolvent or file or consent to the filing of a petition under any bankruptcy or insolvency law or have any such petition filed against it which has not been stayed within sixty (60) days of such filing. During the term of this Agreement, all rights and licenses granted under or pursuant to this Agreement by Isis or Lilly are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that, during the term of this Agreement, the Parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either Party under the U.S. Bankruptcy Code, the Party hereto that is not a party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon written request therefor by the non-subject Party.

8.4 **Termination at Will by Lilly.** Lilly shall have the right to terminate this Agreement at will upon 90 days written notice to Isis.

8.5 **Effect of Termination Due to Lilly Breach, Insolvency or at Will.** If Isis terminates the Agreement based on material breach by or insolvency of Lilly, or if Lilly terminates this agreement at will pursuant to Section 8.4, then:

8.5.1 the licenses granted by Isis to Lilly pursuant to Section 3.1 will terminate, and Lilly will stop making and selling such Product;

8.5.2 any sublicense granted by either Party to any Sublicensee under a license hereunder that terminates as a result of termination of this Agreement by Isis pursuant to Section 8.2 or 8.3 will continue in full force and effect but will be assigned by such Party to the other Party, and such Party will provide the other Party with complete and accurate copies of such sublicense agreements within thirty (30) days following the effective date of such termination; and

8.5.3 Lilly will promptly re-assign any patents assigned to Lilly under this Agreement, and Lilly will assign or otherwise transfer ownership of any regulatory filings related to the Product.

8.6 **Effect of Termination Due to Isis Breach or Insolvency.** If Lilly terminates the Agreement based on material breach by or insolvency of Isis, then:

8.6.1 licenses granted by Isis to Lilly pursuant to Section 3.1 will survive;

8.6.2 Lilly's payment obligations set forth in ARTICLE 4 will continue, *provided, however,* that the amounts of the payments will be decreased to reflect the nature of Isis's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which will be borne by Isis; and

8.6.3 any sublicense granted by either Party to any Sublicensee under a license hereunder that terminates as a result of termination of this Agreement by Lilly pursuant to Section 8.2 or 8.3 will continue in full force and effect but will be assigned by such Party to the other Party, and such Party will provide the other Party with complete and accurate copies of such sublicense agreements within thirty (30) days following the effective date of such termination.

8.7 **Accrued Rights/Surviving Obligations.** Except as expressly provided in this Agreement, expiration or termination of this Agreement will not relieve the Parties of any obligation that accrued prior to such expiration or termination, and Lilly will be obligated to pay and will pay to Isis, within [***] days of such expiration or termination, all payments and royalties due or accrued pursuant to the terms of ARTICLE 4. Upon expiration or early termination of this Agreement, all rights and obligations of the Parties will cease, except as follows:

8.7.1 In the case of expiration of this Agreement only (and, for purposes of clarification, not in the case of termination of this Agreement pursuant to Section 8.2 or 8.3), each of the licenses set forth in Sections 3.1 will survive and will be deemed to be perpetual and fully paid up, provided that all payment and other obligations with respect to such licenses have been fulfilled;

8.7.2 The obligations to pay royalties and other sums accruing hereunder up to the date of termination or expiration will survive;

8.7.3 The obligations of confidentiality set forth in ARTICLE 5 will survive;

8.7.4 The obligations for record keeping and accounting reports set forth in ARTICLE 4 will survive for so long as Products are sold. At such time after termination or expiration of this Agreement when sales or other dispositions of Products have ceased, the Party selling such Product will render a final report along with any royalty payment due;

8.7.5 Isis' and Lilly's rights to inspect books and records as described in ARTICLE 4 will survive;

8.7.6 The obligations of defense and indemnity set forth in ARTICLE 6 will survive;

8.7.7 Any cause of action or claim of Isis or Lilly accrued or to accrue because of any breach or default by the other Party hereunder will survive; and

8.7.8 All other terms, provisions, representations, rights and obligations contained in this Agreement that are intended to survive as specifically set forth elsewhere in this Agreement will survive.

8.8 **Limitation of Liability.** No Party will be liable to another for indirect, incidental, consequential or special damages, including but not limited to lost profits, arising from or relating to any breach of this Agreement, regardless of any notice of the possibility of such damages. Nothing in this Section is intended to limit or restrict the indemnification rights or obligations of any Party under ARTICLE 6.

ARTICLE 9

PUBLICITY

9.1 **Press Release.** Upon execution of this Agreement, the Parties shall issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties.

9.2 **Disclosure of Agreement.** Neither Party to this Agreement may release any information to any Third Party regarding the terms or existence of this Agreement or the reasons for any termination hereof, without the prior written consent of the other Party. Without limitation, this prohibition applies to press releases, educational and scientific conferences, quarterly investor updates, promotional materials, governmental filings and discussions with public officials, the media, security analysts and investors. However, this provision does not apply to any disclosures regarding this Agreement or related information to regulatory agencies such as the FDA or Federal Trade Commission and/or Department of Justice for such disclosures which may be required by law, including requests for a copy of this Agreement or related information by tax authorities. If any Party to this Agreement determines a release of information regarding the existence or terms of this Agreement is required by law (including releases a may be required to be filed through the Securities Exchange Commission or other government agency), that Party will notify the other Party as soon as practicable and give as much detail as possible in relation to the disclosure required. The Parties will then cooperate with respect to determining what information should actually be released. The Parties hereby agree that release of a press release upon complete execution of this Agreement is appropriate and such press release will be mutually agreed upon by the Parties.

9.3 **Use of Names, Logos or Symbols.** No Party hereto will use the name, trademarks, logos, physical likeness, employee names or owner symbol of any other Party for any purpose, including, without limitation, private or public securities placements, without the prior written consent of the affected Party, such consent not to be unreasonably withheld or delayed so long as such use of name is limited to objective statements of fact, rather than for endorsement purposes. Nothing contained herein will be construed as granting either Party any rights or license to use any of the other Party's trademarks or tradenames without separate, express written permission of the owner of such trademark or tradename.

9.4 **Publications.**

9.4.1 On a country by country basis and only with respect to the Major Market Countries, prior to Registration of the Product in such country, (i) Lilly will notify (and provide as much advance notice as possible to) Isis of any event materially related to Product (including the Product's efficacy, safety, clinical data or results, any Registration Submission or Registration) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event; and (ii) Lilly may publish, present or otherwise disclose results regarding the Product to the public at its sole discretion; *however*, any press release or other similar public communication by either Party related to a Product's efficacy, safety, clinical data or results, Registration Submission or Registration, will be submitted to the other Party for review at least 5 Business Days in advance of such proposed public disclosure.

9.4.2 On a country by country basis and only with respect to the Major Market Countries, after Registration of the Product in such country, the appropriateness of all publications regarding development or commercialization of the Products in such country shall be determined by Lilly and Lilly may publish, present or otherwise disclose results regarding the Product to the public at its sole discretion; *however*, in each case Lilly will submit to Isis for review at least 5 Business Days in advance of such proposed public disclosure, any press release or other similar public communication related to new and materially negative information regarding a Product's safety, or clinical data or results.

9.4.3 Notwithstanding the foregoing, the contents of any announcement or similar publicity which has been reviewed and approved by the reviewing Party can be re-released by either Party without a requirement for re-approval.

ARTICLE 10

MISCELLANEOUS

10.1 **Further Assurances, HSR**. Each Party will duly execute and deliver such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary or as the other Party may reasonably request in connection with this Agreement in order to carry out more effectively the provisions and purposes of this Agreement. Each of the Parties shall use its commercially reasonable efforts to take all actions necessary or advisable under applicable laws to consummate and make effective the transactions contemplated by this Agreement including the taking of such reasonable actions as are necessary to obtain any requisite approvals, consents, orders, exemptions or waivers by any governmental authority, including filings pursuant to the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended (the "HSR Act"), if required. The Parties shall make any necessary filings under the HSR Act as soon as practicable, but in any event not more than fifteen (15) days following the Effective Date. In the event the Parties conclude that a filing under the HSR Act is necessary, no payments shall be made and no license granted hereunder shall become effective and, except for this Section 10.1, no time period measured from the Effective Date, shall commence until the applicable waiting period under the HSR Act has expired or been terminated. In the event the applicable waiting period has not expired or been terminated within six months of the Effective Date, either Party shall have the option to terminate this Agreement without liability upon written notice to the other. Neither Party shall be obligated

to agree to any divestiture of assets or limitation on its current or future businesses in connection with obtaining clearance under the HSR Act or other requirement if the Party in good faith believes that the same is unreasonable.

10.2 **Force Majeure.** No Party will be held liable or responsible to the other Party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement (except payment obligations) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party including, but not limited to, fire, flood, earthquake, embargo, war, acts of war or terrorism (whether war be declared or not), insurrection, riot, civil commotion, strike, lockout or other labor disturbance, act of God or act, omission or delay in acting by any governmental authority or the other Party. The affected Party will notify the other Party of such force majeure circumstances as soon as reasonably practical.

10.3 **Assignment.** This Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred, by a Party without the written consent of the other Party; *provided*, *however,* that either Party may, without such consent, (1) assign the Agreement and its rights and obligations hereunder to (i) any wholly-owned subsidiary in a manner such that the assignor (if it continues as a separate entity) will remain liable and responsible for the performance and observance of all its duties and obligations hereunder or (ii) to any successor by merger or sale of substantially all of its business unit to which this Agreement relates, or in the event of its merger or consolidation or Change in Control or similar transaction; or (2) Isis may assign or transfer its rights to receive fees, royalties and milestones under this Agreement (but no liabilities), without Lilly's consent, to a Third Party in connection with a payment factoring transaction. This Agreement will be binding upon the permitted successors and permitted assigns of the Parties. Any assignment not in accordance with this Section 10.3 will be void.

10.4 **Severability.** In the event that any of the provisions contained in this Agreement are held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the Parties. The Parties will replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s), which, insofar as practical, implement the purposes of this Agreement.

10.5 **Notices.** All notices or other communications which are required or permitted hereunder will be in writing and deemed to be effective (a) on the date of delivery if delivered in person and written confirmation of delivery is provided, (b) on the date sent by facsimile or other electronic transmission, provided such receipt is verified, (c) on the day following date of deposit with an overnight courier if a receipt confirming delivery by overnight courier is provided, or (d) three days after mailing if mailed by first-class certified mail, postage paid, to the respective addresses given below, or to another address as it will designate by written notice given to the other Party.

if to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Operating Officer
Telephone: 760-931-9200
Facsimile: 760-918-3592

with a copy to:

Attention: General Counsel
Telephone: 760-931-9200
Facsimile: 760-268-4922

if to Lilly, to:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Group Vice President, Lilly Research Laboratories
with a copy to:

Attention: General Patent Counsel

10.6 **Dispute Resolution.** In the event of any controversy or claim arising from or relating to any provision of this Agreement, or any term or condition hereof, or the performance by a Party of its obligations hereunder, or its construction or its actual or alleged breach, the Parties will try to settle their differences amicably between themselves.

10.7 **Choice of Law.** This Agreement will be governed by and construed in accordance with the laws of the State of New York and the United States without reference to any rules of conflict of laws.

10.8 **Entire Agreement.** This Agreement (including all Schedules hereto), constitute the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangement with respect to the subject matter hereof, whether written or oral. Any amendment or modification to this Agreement will be made in writing signed by both Parties.

10.9 **Headings.** The captions to the several Articles and Sections hereof are not a part of the Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

10.10 **Independent Contractors.** It is expressly agreed that the Parties will be independent contractors and that the relationship between the Parties will not constitute a partnership, joint venture or agency. No Party will have the authority to make any statements,

representations or commitments of any kind, or to take any action, which will be binding on the other Parties, without the prior consent of such other Parties.

10.11 **Further Actions.** Each Party agrees to execute, acknowledge and deliver such further instruments, and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of the Agreement.

10.12 **Waiver.** The waiver by a Party hereto of any right hereunder or the failure to perform or of a breach by another Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

10.13 **Jointly Prepared.** This Agreement has been prepared jointly and will not be strictly construed against either Party.

10.14 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

[THIS SPACE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the Effective Date.

ELI LILLY AND COMPANY

By: _____

ISIS PHARMACEUTICALS, INC.

By: _____
B. Lynne Parshall
Chief Operating Officer and
Chief Financial Officer

[SIGNATURE PAGE TO DEVELOPMENT AND LICENSE AGREEMENT]

List of Schedules

Schedule 1.1 Definitions

Schedule A Isis ASO Compound Patent Rights as of the Effective Date

Schedule B Isis Manufacturing Patent Rights as of the Effective Date

Schedule C Isis Core Technology Patent Rights as of the Effective Date

SCHEDULE 1.1

DEFINITIONS

"Active Program" means with respect to a Product, any [***], of a Product. Without limitation of the generality of the foregoing, for purposes of clarification, research, development and commercialization efforts with respect to a Product will be deemed reasonable if Lilly's research and development efforts with respect to such Product are reasonably comparable with other products in Lilly's portfolio at a similar stage of development, of similar market potential, and presenting similar development or commercialization challenges.

"Affiliate" means any person, organization, corporation or other business entity that controls, directly or indirectly, the power to direct, or cause the direction of, the management and policies of another person, organization, corporation or entity, whether through the ownership of voting securities or by contract or court order or otherwise. For purposes of this definition, an entity will be deemed to control another entity if it owns or controls, directly or indirectly, at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors or their equivalent of such other entity. Regulus Therapeutics Inc. will not be considered an Affiliate of Isis.

"ASO Compound" means an [***].

"ASO Field" means the development, manufacture and sale of ASO Products for all uses.

"Calendar Quarter" will mean the respective three month periods ending on March 31, June 30, September 30, or December 31 for so long as the Agreement is in effect.

"Calendar Year" will mean each successive twelve month period commencing on January 1 and ending on December 31 for so long as the Agreement is in effect.

"Change in Control" means any of the following events: (i) the acquisition by any Person or group, other than a Person or group controlling such Party as of the Effective Date, of "beneficial ownership" (as defined in Rule 13d-3 under the United States Securities Exchange Act of 1934, as amended), directly or indirectly, of fifty percent (50%) or more of the shares of such Party's capital stock the holders of which have general voting power under ordinary circumstances to elect at least a majority of such Party's Board of Directors or equivalent body (the ***"Board of Directors"***) (the ***"Voting Stock"***); (ii) the first day of which less than two-thirds of the total membership of such Party's Board of Directors will be Continuing Directors (as such term is defined below); (iii) the approval by the shareholders of such Party of a merger, share exchange, reorganization, consolidation or similar transaction of such Party (a ***"Transaction"***), other than a Transaction which would result in the Voting Stock of such Party outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity) more than fifty percent (50%) of the Voting Stock of such Party or such surviving entity immediately after such Transaction; or (iv) approval by the shareholders of such Party of a complete liquidation of such Party or a sale or disposition of all or substantially all of the assets of such Party. For purposes of this

definition, "Continuing Directors" means individuals serving as of the Second Restatement Date hereof on such Party's Board of Directors and any individuals elected after the date hereof whose election or nomination was approved by at least a majority of the Continuing Directors serving at the time.

"Compulsory License" means, in the case of Product, a compulsory license under the a Party's technology obtained by a Third Party through the order, decree or grant of a governmental authority having competent jurisdiction, authorizing such Third Party to manufacture, use, sell, offer for sale or import such Product in a particular country.

"Confidential Information" means any and all inventions, know-any, and data and will include, without limitation, information relating to research and development plans, experiments, results and plans, compounds, therapeutic leads, candidates and products, clinical and preclinical data, trade secrets and manufacturing, marketing, financial, regulatory, personnel and other business information and plans, all scientific, clinical, regulatory, marketing, financial and commercial information or data, all whether communicated in writing, orally or by any other means, and which is provided by one Party to the other Party in connection with this Agreement. Confidential Information will not include information that:

(a) is known by the receiving Party at the time of its receipt, and not through a prior disclosure by the disclosing Party, as documented by written records;

(b) is properly in the public domain through no fault of the receiving Party;

(c) is subsequently disclosed to the receiving Party by a Third Party who may lawfully do so and is not under an obligation of confidentiality to the disclosing Party; or

(d) is developed by the receiving Party independently of Confidential Information received from the other Party, as documented by written records.

"Control" or ***"Controlled"*** means with respect to any intellectual property right, that the Party owns or has a license to such intellectual property right and has the ability to grant access, a license, or a sublicense to such intellectual property right to the other Party as provided for in this Agreement without violating an agreement with, or infringing any rights of, a Third Party as of the time the Party would be first required under this Agreement to grant the other Party such access, license or sublicense.

"Cover" (including variations thereof such as ***"Covering"***, ***"Covered"***, and ***"Coverage"***) means that the manufacture, use, import, offer for sale or sale of a Product would infringe a Valid Claim; provided, with respect to a process or manufacturing patent, that such a Valid Claim therein effectively precludes a Third Party from manufacturing, using, importing, offering for sale, or selling such Product. The determination of whether a Product is Covered by a particular Valid Claim will be made on a country-by-country basis. A Valid Claim will be deemed to provide effective preclusion hereunder where (i) there is no competing product being marketed or (ii) if a product is being marketed by a competitor, it infringes the Valid Claim (including any period in which, and provided that, the Valid Claim is being litigated).

"CPI" or ***"Consumer Price Index"*** means the consumer price index for all urban consumer series ID CUUR0000SAO as published from time to time by the US Bureau of Labor Statistics, where the CPI for June, 2001 was 178.

"Effective Date" has the meaning ascribed to it in the preamble.

"eIF-4E" means eukaryotic initiation factor-4E (Entrez Gene ID: 1977).

"eIF-4E Compound" means [***] of the [***] that are [***] eIF-4E [***] eIF-4E [***].

"FDA" means the United States Food and Drug Administration or any successor agency having the administrative authority to regulate the approval for marketing of new human pharmaceutical or biological therapeutic products in the United States.

"First Commercial Sale" means with respect to any Product the first sale to a Third Party by Lilly, its Affiliates or Sublicensees. First Commercial Sale will not include transfer of reasonable quantities of any free samples of a Product or reasonable quantities of a Product solely for development purposes, such as for use in experimental studies or clinical trials. First Commercial Sale with respect to an Indication means the First Commercial Sale following receipt of regulatory approval to include such Indication in the official labeling for the Product.

"[***] Agreement" means that certain agreement between [***] and [***]effective [***], and any amendments thereto.

"IND" means an Investigational New Drug application as defined in 21 C.F.R. 312 and any versions thereof governing the FDA as may be amended from time to time.

"Indication" means, with respect to a Product, such Product's interference with a gene to affect a specific primary endpoint of a pathophysiologic state, regardless of etiology. For purposes of clarity, if an Indication was not included in a particular NDA (or any foreign counterpart or equivalent section) for a Product but is included in a subsequent NDA (or abbreviated NDA or supplemental NDA) for such Product, such Indication is presumptively a separate and distinct "Indication" from all other Indications for such Product.

"Initiate" means with respect to a clinical study, the initial dosing of the first patient in such study.

"Institutional Review Board" means an Institutional Review Board as defined in 21 C.F.R. 56 as may be amended from time to time, or its applicable foreign equivalent.

"Isis ASO Compound Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that Cover the composition of matter of a Product or the method of using such Product *per se*. A representative list of the Isis ASO Compound Patent Rights as of the Effective Date is attached to this Agreement as ***Schedule A***.

"Isis Core Technology Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that Cover the practice of Isis Standard Chemistry including Patent Rights that Cover chemistries, motifs (patterns of arranging the chemical building blocks of an antisense oligonucleotides) and/or cellular mechanism of action by which an oligonucleotide promotes RNA cleavage. A representative list of the Isis Core Technology Patent Rights that exist as of the of this Agreement are listed in ***Schedule C***.

"Isis Know-How" means all Know-How that is either (i) Controlled by Isis as of the Effective Date or (ii) that becomes Controlled by Isis after the Effective Date that is reasonably necessary or useful for research, development, manufacture, use and sale of Products.

"Isis Manufacturing Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that Cover the practice of the Isis Standard Chemistry Manufacturing Process. The Isis Manufacturing Patent Rights as of the date of this Agreement are listed in ***Schedule B***.

"Isis Patent Rights" means the Isis Core Technology Patent Rights, the Isis Manufacturing Patent Rights and Isis ASO Compound Patent Rights. To the extent Isis Controls Patent Rights as of the Effective Date other than the Isis Manufacturing Patents, Isis Core Technology Patent Rights, and the Isis ASO Compound Patent Rights, and such Patent Rights would Cover a Product, such Patent Rights will be included in the definition of Isis Patent Rights automatically if they can be licensed to Lilly with no obligation (financial or otherwise) to any Third Party with respect to a Product. To the extent Isis Controls Patent Rights as of the Effective Date, other than the Isis Manufacturing Patent Rights, the Isis Core Technology Patent Rights and Isis ASO Compound Patent Rights that would Cover a Lilly ASO Product, and such Patent Rights were acquired by Isis from a Third Party and/or Isis has obligations (financial or otherwise) to a Third Party in connection with the practice of such Patent Rights, such Patent Rights will only be included in the definition of Isis Patent Rights if Isis and Lilly negotiate an agreement to license such Patent Rights which includes (1) the assumption by Lilly of all financial obligations of Isis arising from the grant to Lilly and the practice by Lilly, its Affiliates of Sublicensees, of the Patent Rights, (2) the compensation of an appropriate portion of any acquisition costs incurred by Isis in connection with obtaining Control of such Patent Rights, and (3) an agreement by Lilly to abide by all of the terms of the agreement under which Isis has obtained Control of such Patent Right. For purposes of determining whether a royalty is payable under Section 4.4 Isis Patent Rights will include any Patent Right assigned to Lilly under Section 7.2.

"Isis Standard Chemistry" means "2´MOE Gapmers" or an antisense phosphothioate oligonucleotide of [***] nucleotides wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and a stretch of at least [***] consecutive nucleotides remain unmodified (deoxy sugars) and the remaining nucleotides contain an O´-methyl O´-ethyl substitution at the 2´ position (MOE).

"Isis Standard Chemistry Manufacturing Process" means the manufacturing process as of the [***], represented by the batch record for Isis [***]. Manufacturing for this purpose includes [***].

"Isis Technology" means Isis Know-How and Isis Patent Rights.

"Know-How" means all tangible or intangible know-how, inventions (whether patentable or not), discoveries, processes, formulas, data, clinical and preclinical results, non-patented inventions, trade secrets, and any physical, chemical, or biological material or any replication of any such material in whole or in part.

"[***] Market Type(s)" means any of [***]

"License Option Agreement" has the meaning set forth in Recital C.

"Major Market Country" means the [***].

"NDA" means a new drug application or other application filed with the FDA to obtain approval for marketing a Product in the United States, or any future equivalent process.

"Net Royalty" means the effective royalty rate payable to a Party hereunder determined by subtracting from the actual royalty rate set forth in Section 4.4 hereof the royalty that such Party is required to pay to a Third Party licensor, including, without limitation, under the [***] Agreement or the [***] Agreement.

"Net Sales" means, with respect to a Product, the gross amount invoiced by a Party, its Affiliates or Sublicensees thereof to unrelated Third Parties, excluding any Sublicensee, for the Product, less:

(a) Trade, quantity and cash discounts allowed;

(b) Commissions, discounts, refunds, rebates, chargebacks, retroactive price adjustments, and any other allowances which effectively reduce the net selling price;

(c) Product returns and allowances;

(d) That portion of the value associated with the cost of the drug delivery systems;

(e) Any tax imposed on the production, sale, delivery or use of the Product, including, without limitation, sales, use, excise or value added taxes;

(f) Allowance for distribution expenses; and

(g) Any other similar and customary deductions.

Net Sales will be calculated in U.S. Dollars. Such amounts will be determined from the books and records of a Party, its Affiliate or Sublicensee, maintained in accordance with U.S. Generally Accepted Accounting Principles or, in the case of Sublicensees, such similar accounting principles, consistently applied. Each Party further agrees in determining such amounts, it will use its then current standard procedures and methodology, including its then current standard exchange rate methodology for the translation of foreign currency sales into U.S. Dollars or, in the case of Sublicensees, such similar methodology, consistently applied.

Net Sales excludes:

(i) The transfer of reasonable and customary quantities of free samples of Product(s) and the transfer of Product(s) as clinical trial materials, other than for subsequent resale;

(ii) Sales or transfers of Product(s) among a Party and its Affiliates unless the receiving Party is the consumer or user of the Product(s); and

(ii) Use by a Party or its Affiliates or Sublicensees of Product for any use connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary marketing approvals for Product (unless such Product is subsequently sold).

In the event that the Product(s) is sold as part of a Combination Product (where ***"Combination Product"*** means any pharmaceutical product which comprises the Product(s) and at least one other active compound(s) and/or ingredients), the Net Sales of the Product(s), for the purposes of determining royalty payments, will be determined by multiplying the Net Sales of Combination Product (as defined in the standard Net Sales definition) by the fraction, A / (A+B) where A is the weighted average sale price of the Product(s) when sold separately in finished form, and B is the weighted average sale price of the other product(s) sold separately in finished form.

In the event that the weighted average sale price of the Product(s) can be determined but the weighted average sale price of the other product(s) cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the fraction A / C where A is the weighted average sale price of the Product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of the other product(s) can be determined but the weighted average sale price of the Product cannot be determined, Net Sales for purposes of determining royalty payments will be calculated by multiplying the Net Sales of the Combination Product by the following formula: one (1) minus B / C where B is the weighted average sale price of the other product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of both the Product(s) and the other product(s) in the Combination Product cannot be determined, the Parties will attempt to agree on an appropriate weighted average

sale price of both the Product(s) and the other product(s) in the Combination Product, and lacking such agreement the Net Sales of the Product(s) will be deemed to be equal to fifty percent (50%) of the Net Sales of the Combination Product.

The weighted average sale price for a Product, other product(s), or Combination Product will be calculated once each Calendar Year and such price will be used during all applicable royalty reporting periods for the entire Calendar Year. When determining the weighted average sale price of a Product, other product(s), or Combination Product, the weighted average sale price will be calculated by dividing the sales dollars (translated into U.S. Dollars) by the units of active ingredient sold during the twelve (12) months (or the number of months sold in a partial Calendar Year) for the respective Product(s), other product(s), or Combination Product. In the initial Calendar Year, a forecasted weighted average sale price will be used for Product(s), other product(s), or Combination Product. Any over or under payment due to a difference between

forecasted and actual weighted average sale prices will be paid or credited in the first royalty payment of the following Calendar Year.

"[***] Agreement" means that certain agreement between [***] effective [***] and all amendments thereto.

"Option Exercise Date" has the meaning set forth in Recital D.

"Patent Rights" means: (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; (d) any reissues, substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecutions, continuations-in-part, or divisions of or to any of the foregoing; and (e) term extension or other governmental action which provide exclusive rights beyond the original patent expiration date.

"Phase II Study" means a human clinical trial conducted on a series of patients with the same type of cancer, in each case where the protocol for such phase II study was approved by the applicable Institutional Review Board.

"Phase III Study Initiation" means the dosing of the first patient in the first human clinical trial conducted in patients and designed to establish Product safety and efficacy and required to obtain clinical registration of a product with health regulatory authorities such as the FDA.

"Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains an eIF-4E Compound.

"Registration" means (a) in the United States, approval by the FDA of an NDA, or similar application for marketing approval, and satisfaction of any related applicable FDA registration and notification requirements (if any), and (b) in any Major Market Country other than the United States, approval by regulatory authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA and satisfaction of any related applicable regulatory and notification requirements, if any, together with any other approval necessary to make and sell pharmaceuticals and medical devices commercially in such country.

"Registration Submission" means (a) in the United States, acceptance by the FDA of the filing of an NDA, or similar application for marketing approval, for the Product, and (b) in any Major Market Country other than the United States, the filing with the applicable Regulatory Authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA for the Product.

"***RNAi Compound***" means [***]

"[***] Market Types" means any [***] that are not [***] Market Types.

"Sublicensees" means any Third Party to which Lilly or any of its Affiliates or Isis or any of its Affiliates grants any right to manufacture, market and sell a Product. A Third Party who is granted only the right to sell a Product (such as a wholesaler) will not be considered a Sublicensee.

"Territory" means the entire world.

"Third Party" means any Party other than Isis or Lilly and their respective Affiliates.

"Upstream Licenses" means those Third Party licenses or sublicenses listed on Schedule .

"Valid Claim" means any claim in an issued and unexpired patent which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction following exhaustion of all possible appeal processes and which has not been admitted to be invalid or unenforceable through reissue, reexamination or disclaimer, or otherwise.

SCHEDULE A

ISIS ASO COMPOUND PATENT RIGHTS AS OF THE EFFECTIVE DATE

SCHEDULE B

ISIS MANUFACTURING PATENT RIGHTS AS OF THE EFFECTIVE DATE

SCHEDULE C

ISIS CORE TECHNOLOGY PATENT RIGHTS AS OF THE EFFECTIVE DATE

AMENDED & RESTATED LICENSE AGREEMENT

THIS AMENDED & RESTATED LICENSE AGREEMENT (the "***Agreement***") is made and entered into effective as of November 30, 2009 (the "***Restatement Date***"), by and between **ATLANTIC PHARMACEUTICALS LIMITED (**formerly **ATLANTIC HEALTHCARE (UK) LIMITED** registered number 6025726), whose registered office is MoFo Notices Limited, 7th Floor, City Point, One Ropemaker Street, London EC2Y 9AW ("***Atlantic***") and **ISIS PHARMACEUTICALS, INC.**, having principal offices at 1896 Rutherford Road, Carlsbad, CA 92008 ("***Isis***"). Atlantic and Isis each may be referred to herein individually as a "***Party***," or collectively as the "***Parties***."

WHEREAS, Isis and Atlantic are parties to the License Agreement dated March 7, 2007, as amended December 6, 2007 and December 18, 2008 (as amended, the "***Original Agreement***") under which Isis, among other things, licensed to Atlantic the drug known as Alicaforsen (also known as ISIS 2302) for Atlantic to develop and commercialize, together with, at Atlantic's election, the right to license second generation ICAM-1 products;

WHEREAS, Isis and Atlantic now desire to amend and restate the Original Agreement in order to, among other things, redefine and confirm as of the Restatement Date each Party's rights and obligations with respect to the development, manufacture, and commercialization of Alicaforsen Products, and to return to Isis all other rights granted to Atlantic under the Original Agreement; and

NOW, THEREFORE, the Parties do hereby agree as follows:

ARTICLE 1 -

DEFINITIONS; AMENDMENT AND RESTATEMENT; REVERSION OF RIGHTS; DATA ASSIGNMENT TO ISIS

Section 1.1 **Definitions.**

1.1.1 Capitalized terms used in this Agreement and not otherwise defined herein have the meanings set forth in Appendix 1.

Section 1.2 **Amendment and Restatement; Reversion of Rights; Data Assignment to Isis.**

1.2.1 Amendment and Restatement; Reversion of Rights. Effective as of the Restatement Date, notwithstanding anything to the contrary in the Original Agreement (i) this Agreement restates, supersedes, and terminates the Original Agreement in its entirety, and (ii) except as otherwise expressly provided in this Agreement, the Original Agreement (including all licenses and other rights granted thereunder) is deemed void *ab initio*. Therefore, for the

avoidance of doubt, (x) any rights and licenses granted by Isis to Atlantic under the Original Agreement and not expressly granted by Isis to Atlantic under this Agreement (the "***Reverted Rights***"), automatically revert back to Isis as of the Restatement Date as though such licenses and rights were never granted to Atlantic under the Original Agreement, and (y) that certain Subscription and Share Exchange Agreement dated March 16, 2007 (the "***Subscription and Share Exchange Agreement***") will (A) be unaffected by the termination of the Original Agreement, and (B) continue in full force and effect in accordance with its terms. Atlantic agrees, at Isis' request and expense, to execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Isis may reasonably request for use in applying for, obtaining, confirming, sustaining and/or enforcing Isis' rights relating to such Reverted Rights.

1.2.2 Assignment of Isis Data to Isis. Effective as of the Restatement Date, Atlantic hereby assigns to Isis all of Atlantic's right, title and interest in and to (i) the Isis Data, and (ii) any other Regulatory Documentation, data, results and information related to testing and studies of Alicaforsen (including clinical data, analytical test results and non-clinical pharmacology and safety data) in the possession of Atlantic on the Restatement Date, to the extent necessary for the development and commercialization of products covered by the Reverted Rights. In the event any of the Isis Data and any other Regulatory Documentation, data, results and information related to testing and studies of Alicaforsen can be used for development and commercialization of both Alicaforsen Products and products covered by the Reverted Rights, then such data shall not be assigned by Atlantic to Isis, however, Isis shall have a non-exclusive, royalty-free, fully-paid up, worldwide license to use such data for products covered by the Reverted Rights.

ARTICLE 2 -
ALICAFORSEN GRANT OF RIGHTS

Section 2.1 **Alicaforsen License Grant.**

2.1.1 Subject to the terms and conditions of this Agreement, Isis hereby grants to Atlantic:

(i) an exclusive, worldwide license under the Alicaforsen Patents and the ICAM-1 Specific Patents solely to develop, make, have made, use, sell, offer for sale, have sold and import Alicaforsen API and Alicaforsen Products. The license granted to Atlantic under this Section 2.1.1(i) is sublicensable only in connection with a license of rights to an Alicaforsen Product to a Third Party for the continued development, manufacture and commercialization of that Alicaforsen Product in accordance with the terms of this Agreement; and

(ii) a non-exclusive, worldwide license under the Excluded Manufacturing IP solely to make and have made Alicaforsen API. The license granted to Atlantic under this Section 2.1.1(ii) is sublicensable to a Third Party for the manufacture of Alicaforsen API in accordance with the terms of this Agreement.

Section 2.2 **Data Transfer**.

2.2.1 After the Effective Date, Isis transferred and assigned to Atlantic all of Isis' right, title and interest in and to (i) the Regulatory Documentation, data, results and information related to testing and studies of Alicaforsen (including clinical data, analytical test results and non-clinical pharmacology and safety data) in the possession of Isis on the Effective Date to the extent such data, results and/or information were necessary for the continued development and commercialization of Alicaforsen ("***Isis Data***"), and (ii) the know how which was owned by or licensed to Isis at the Effective Date that related to the formulation of Alicaforsen from Alicaforsen API, *but excluding* the Excluded Manufacturing IP (the "***Isis Manufacturing Know How***"). As of the Restatement Date, Atlantic will use such Isis Data and Isis Manufacturing Know How solely to the extent necessary to manufacture, develop and/or commercialize Alicaforsen API and/or Alicaforsen Products.

Section 2.3 **No Implied Licenses.** All rights in and to the Alicaforsen Patents, the ICAM-1 Specific Patents, and the Excluded Manufacturing IP not expressly licensed to Atlantic under Section 2.1, and any other Patents or know-how of Isis or its Affiliates, are hereby retained by Isis or its Affiliates. Except as expressly provided in Section 2.1, Isis will not be deemed by estoppel or implication to have granted Atlantic any license or other right with respect to any intellectual property of Isis. Nothing in this Agreement will prevent Isis from practicing the Alicaforsen Patents, the ICAM-1 Specific Patents, or the Excluded Manufacturing IP for products other than Alicaforsen Products.

ARTICLE 3 - ATLANTIC PRODUCT DEVELOPMENT

Section 3.1 **Development/Commercialization/Regulatory Responsibilities.**

3.1.1 **Commercially Reasonable Efforts.** Unless Isis exercises its reversion rights under Section 11.2, Atlantic is fully responsible for the continued development and commercialization of Alicaforsen Products and will use Commercially Reasonable Efforts to develop Alicaforsen Products for all commercially reasonable indications, including Alicaforsen Products for the treatment of Pouchitis and to make its First Commercial Sale of an Alicaforsen Product for the treatment of Pouchitis in the USA and Europe as soon as practicable. Atlantic hereby assumes all regulatory responsibilities in connection with Alicaforsen Products, including sole responsibility for all related Regulatory Documentation and for obtaining all Regulatory Approvals. Atlantic will comply with all Applicable Laws and the Quality Standard in connection with the development and commercialization of Alicaforsen Products. For the avoidance of doubt, any sublicensee that enters into a Sublicense with Atlantic will use Commercially Reasonable Efforts in accordance with this Agreement to develop and commercialize any Alicaforsen Products that are the subject of such Sublicense, and Atlantic will ensure that such efforts are undertaken.

3.1.2 **Development Plan.** Without limiting any of the foregoing in Section 3.1.1, Atlantic will use Commercially Reasonable Efforts to implement and perform the initial Development Plan approved by both Atlantic and Isis as attached to this Agreement as Appendix 4 (the "***Initial Development Plan***"), which contains a Gantt chart of Atlantic's good-faith development plan for Alicaforsen as of the Restatement Date which supersedes all previous

development plans. Atlantic may update the Initial Development Plan within 30 days following the Restatement Date so long as (i) any such update does not constitute a material modification of, or addition to, the Initial Development Plan, and (ii) Atlantic promptly provides Isis with a copy of such modified Initial Development Plan with a summary/explanation of any modifications thereto. Following the Restatement Date, Atlantic will use Commercially Reasonable Efforts to arrange and participate in "advisory" meetings with the FDA and EMEA (or any other Regulatory Authority) as soon as practicable (each, an "***Advisory Meeting***"), and following each such Advisory Meeting, Atlantic will present the information arising from such meeting(s) to the JDC to, among other things, discuss any necessary modifications to the Development Plan. The Development Plan will be updated and modified only as determined by the JDC on a periodic basis under Section 3.2.1, including following the occurrence of any Advisory Meetings held between Atlantic and the FDA and/or the EMEA (or any other Regulatory Authority). Notwithstanding the foregoing, any Development Plan to be performed by one of Atlantic's sublicensees under a Sublicense will not require the approval of the JDC so long as (i) such Development Plan is provided to the JDC for the JDC's review and comment and such sublicensee considers in good faith any comments provided by the JDC, (ii) such Development Plan is not in conflict with the terms and conditions of this Agreement, and (iii) such sublicensee uses Commercially Reasonable Efforts to implement and perform such Development Plan.

Section 3.2 **Joint Development Committee.**

3.2.1 To promote the successful development of the Alicaforsen Products, the Parties will establish a Joint Development Committee (the "***JDC***"), which will be formed and will hold its first meeting within 90 days after the Restatement Date, and will be comprised of two Isis representatives and two Atlantic representatives ("***Committee Members***"). A Party may replace any of its Committee Member(s) by notice to the other Party. Each Committee Member shall be appropriately qualified and experienced in order to make a meaningful contribution to JDC meetings. The purpose of the JDC is to provide a forum for the Parties to share information and knowledge on the on-going research and development of the Alicaforsen Products, including sharing scientific direction and data, discussing the current development and regulatory status of the Alicaforsen Products, any Alicaforsen Product sublicensing development plans with Third Parties, discussing regulatory or quality assurance issues in relation to the Alicaforsen API, and reviewing, providing advice on, and approving the Development Plan. In addition, at JDC meetings, Isis will apprise the JDC of any development activities undertaken by Isis with respect to any Follow-On Products. The JDC shall conduct its discussions in good faith with a view to operating to the mutual benefit of the Parties and in furtherance of the successful marketing of Alicaforsen Products. The JDC shall meet at Isis' corporate offices located in Carlsbad, California, USA where such meeting is not held by video-conference or telephone conference, as often as the Committee Members may determine but in any event not less than once per calendar quarter. Each JDC meeting shall be chaired by a Committee Member nominated by Atlantic and Atlantic is responsible for coordinating and ensuring that such communication and meetings take place in a timely manner in accordance with this Agreement, and Isis shall co-operate with Atlantic and will not unreasonably refuse requests for such meetings. The JDC will strive to make decisions by majority vote, and record such decisions in the minutes of the applicable JDC meeting. If, after good faith discussions, the JDC is unable to decide a particular matter by majority vote, such matter will be referred to the Executive Officers for final resolution. If the matter is not resolved by the Executives Officers within 30 days, either Party may seek final resolution of the matter in accordance with Section 14.4.

3.2.2 The JDC will continue in existence for three years after the Restatement Date, subject to extension by mutual agreement of the Parties.

Section 3.3 **Safety Database**.

3.3.1 Isis maintains a database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Isis Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, Atlantic will cooperate in connection with populating the Isis Database. Atlantic will provide Isis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to each Alicaforsen Product as soon as practicable following the date such information is available to Atlantic (but not later than 30 days after Atlantic's receipt of such information). In addition, in connection with any reported serious adverse event, Atlantic will provide Isis (promptly following such event and prior to any communication with a Regulatory Authority or ethics committee) in a mutually acceptable format, the following patient data where it is reasonably available to Atlantic once informed of a serious adverse event and any other data Atlantic reasonably deems relevant to the Isis Database: (a) basic statistics (including age, race, gender, weight, height); (b) medical history; (c) concurrent medication usage; (d) particulars of the event (verbatim term, MedDRA term & system organ class, onset date, resolution date, relation to Alicaforsen Product, severity/seriousness, outcome); (e) dosing history (dates, quantity of Alicaforsen Product administered, method of administration); (f) chemistry and hematology lab tests; and (g) ocular pressure. Atlantic will deliver all such information to Isis for the Isis Database to: Isis Pharmaceuticals, Inc. 1896 Rutherford Road, Carlsbad, California 92008, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). For clarity, Atlantic shall be responsible for all safety and/or pharmacovigilance matters relating to or arising from the development and commercialization of the Alicaforsen Products and for making all adverse event reports to the relevant Regulatory Authorities at the times and in the manner it deems appropriate to comply with all Applicable Laws.

3.3.2. From time to time, Isis utilizes the information in the Isis Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of antisense oligonucleotides, including with respect to safety. As such, if and when Isis identifies safety or other related issues that Isis reasonably believes may be relevant to an Alicaforsen Product or the gene target, ICAM-1 (including any potential class-related toxicity), Isis will promptly inform Atlantic of such issues and, if requested, provide the data supporting Isis' conclusions. In addition, if Isis becomes aware of any serious adverse events related to Alicaforsen or ICAM-1, Isis will promptly inform Atlantic. Isis will deliver all such information to Atlantic to: Atlantic Pharmaceuticals Limited, Maple House, Birdbrook, Halstead, CO9 4BB, UK, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Atlantic).

Section 3.4 **Reports.** Atlantic agrees to keep Isis informed with respect to activities and progress with the further development and commercialization of Alicaforsen Products (including with respect to the activities of Atlantic's Affiliates and sublicensees), and agrees to provide to Isis and the JDC every six months a summary of such activities and progress. In accordance with Section 3.2.1, during the period Atlantic has a right of first negotiation under Section 4.1, Isis agrees to keep Atlantic informed with respect to Isis' activities and progress with the further development and commercialization of Follow-On Products by providing a summary of any such activities at meetings of the JDC.

Section 3.5 **[Not used]**

Section 3.6 **Supply of Existing Alicaforsen API.**

3.6.1 Isis agrees to supply Atlantic with a quantity of Alicaforsen API that is in Isis' possession as of the Restatement Date, reasonably sufficient to obtain Regulatory Approval for an Alicaforsen Product for Pouchitis (but not to exceed [***] kg) in the USA or Europe [***], in accordance with a clinical trial program set forth in the Development Plan. For the avoidance of doubt, the [***] kg of Alicaforsen API supplied by Isis prior to the Restatement Date has been supplied [***].

3.6.2 Atlantic and Isis agree that, to the extent available from the stocks of Alicaforsen API in Isis' possession as of the Restatement Date, any other quantities of Alicaforsen API required by Atlantic for the development and commercialization of Alicaforsen Product may be purchased from Isis in a minimum order size of [***]kg at a cost of [***] Dollars ($[***]) per gram until such stocks have been exhausted. As of the Restatement Date, Isis has approximately (i) [***] kilograms of Alicaforsen API available for sale, and (ii) [***] kilograms of Alicaforsen API in quarantine with the possibility of release from such quarantine if certain qualification study(ies) are performed (*e.g.*, a bridging toxicology study). Isis will hold such Alicaforsen API in quarantine for a period of [***] ([***]) years after the Restatement Date for the benefit of Atlantic. If Atlantic has the necessary study(ies) performed, at Atlantic's expense, and such Alicaforsen API is successfully released from quarantine in accordance with cGMP, Isis will sell such [***] kilograms of Alicaforsen API to Atlantic at a cost of [***] Dollars ($[***]) per gram.

3.6.3 All Alicaforsen API ordered by Atlantic pursuant to Section 3.6 will be shipped by Isis to Atlantic, EXW (Incoterms 2000) Isis' premises, to the destination specified in writing by Atlantic. All transportation and insurance costs are the sole responsibility of Atlantic. Isis warrants that each such amount of Alicaforsen API supplied by Isis pursuant to Section 3.6; (i) will have been manufactured in accordance with cGMP, (ii) meets the specification for Alicaforsen API set out in the Regulatory Documentation existing at the Restatement Date, (iii) have at least [***] months shelf life remaining when delivered, and will be accompanied by a certificate of analysis.

Section 3.7 **Product Manufacturing Responsibility.** Except as otherwise provided in this Agreement, Atlantic acknowledges and agrees that it is solely responsible for the manufacturing of Alicaforsen Product and Alicaforsen API, including, without limitation, management of the overall manufacturing strategy and tactics, CMC work, validation activities

and batches, formulation, contract manufacturer selection for finished Alicaforsen Product, associated audits, and stability testing. For the avoidance of doubt, except as expressly set forth in Section 3.6.1 and Section 3.6.2 of this Agreement, neither Atlantic nor Isis will have any obligations to one another with respect to the manufacture or supply of Alicaforsen API or Alicaforsen Product, and Atlantic is licensed under Section 2.1.1 to make and/or have made Alicaforsen API and Alicaforsen Product itself or by a Third Party, including, without limitation, by an Enabled CMO.

ARTICLE 4 - FOLLOW-ON PRODUCT ROFN; EXCLUSIVITY COVENANTS

Section 4.1 **(a) Follow-On Product ROFN.** For a period of [***] ([***]) years following the Restatement Date, if Isis desires to (i) offer a Third Party an exclusive license to the rights to Systemic Delivery and Enema Delivery for a Follow-On Product (the "***Follow-On Product License***"), or (ii) pursue a bona-fide offer from a Third Party for a Follow-On Product License, then Isis will provide Atlantic with the right of first negotiation for such Follow-On Product License by written notice to Atlantic and will promptly deliver evaluation materials and any data reasonably relevant to such Follow-On Product, at which time Atlantic will have [***] days to notify Isis in writing whether Atlantic desires to obtain the Follow-On Product License. If Atlantic provides Isis with timely written notice within such [***]-day period that Atlantic desires to obtain the Follow-On Product License, then Isis and Atlantic will negotiate in good faith, to conclude a written license agreement within [***] days on commercially reasonable terms (including Development Plan and funding commitments from Atlantic for such Follow-On Product). If Atlantic fails to notify Isis within such [***]-day period that Atlantic desires to obtain the Follow-On Product License or, if despite good faith negotiations Atlantic and Isis are unable to reach agreement within [***] days after Isis' receipt of such notice from Atlantic, then, notwithstanding anything to the contrary in this Agreement, (i) Isis will be free to develop and commercialize the Follow-On Product on its own or with a Third Party and may grant the Follow-On Product License (or grant a right to obtain such an exclusive license) to any Third Party for any indication on economic terms which, when taken as a whole, are no more favorable to any such Third Party than the terms last offered under this Section 4.1 by Atlantic to Isis, (ii) Atlantic will have no further rights to such Follow-On Product, and (iii) Isis will have no further obligations to Atlantic under this Agreement with respect to such Follow-On Product.

(b) [***] Standstill Period. Notwithstanding the foregoing in Section 4.1, for a period of [***] ([***]) years following the Restatement Date (the "***Standstill Period***"), Isis agrees (i) not to consummate a Follow-On Product License with a Third Party that includes a license to develop and commercialize a Follow-On Product intended to achieve a therapeutic effect in the [***] ("***[***]***"), or (ii) if Isis consummates such a Follow-On Product License that includes rights to develop and commercialize a [***], such Third Party will be precluded from undertaking development of the [***] during the Standstill Period. For purposes of this Section 4.1(b), a Third Party will be deemed to have initiated development of a [***] if such Third Party initiates [***] with a Follow-On Product intended to achieve a therapeutic effect in the [***].

Section 4.2 **Exclusive Partner.**

4.2.1 During the Term of this Agreement so long as Atlantic is developing and commercializing Alicaforsen Products in accordance with the terms of this Agreement, Isis will not develop or commercialize itself, and will not permit or grant any license under the Alicaforsen Patents or the ICAM-1 Specific Patents to a Third Party to develop or commercialize, any antisense drug compound designed to directly inhibit ICAM-1. Notwithstanding the foregoing, subject to Section 4.1, Isis retains the right to (i) use antisense compounds modulating ICAM-1 (including Alicaforsen) or to transfer such antisense compounds to Third Parties in each case for non-commercial target validation purposes, and (ii) use, manufacture, research, develop, and commercialize Follow-On Products and any other compounds to inhibit ICAM-1 other than Alicaforsen Products, covered by any of Isis' intellectual property (including the Reverted Rights), and such activities will not be interpreted as a breach of this Agreement. For the avoidance of doubt, subject to Section 4.1, Isis shall not be prohibited in any manner from using or exploiting any Isis intellectual property (including the Reverted Rights) with products and compounds other than Alicaforsen Products. Isis' obligations under this Section 4.2.1 will automatically terminate in the event of a Discontinuance.

4.2.2 To avoid confusion in the marketplace, during the term of this Agreement, Atlantic agrees not to develop or commercialize any product designed to directly inhibit ICAM-1 other than the Alicaforsen Products, and will not permit or grant any license under the Alicaforsen Patents or ICAM-1 Specific Patents to a Third Party to develop or commercialize any such product other than the Alicaforsen Products. Notwithstanding the foregoing sentence, in the event that Atlantic's right of first negotiation for the Follow-On Product License under Section 4.1(a) (i) is voluntarily terminated by Atlantic by written notice to Isis, or (ii) terminates in accordance with Section 4.1(a) and Atlantic and Isis have not consummated the Follow-On Product License, this Section 4.2.2 will no longer apply to Atlantic.

ARTICLE 5 - [Not used]

ARTICLE 6 - FINANCIAL PROVISIONS

Section 6.1 **Up-Front Payment by Atlantic.**

6.1.1 In consideration of the licenses granted to Atlantic under the Original Agreement and Section 2.1.1 of this Agreement, following the Effective Date, Isis and Atlantic executed the Subscription and Share Exchange Agreement, pursuant to which Atlantic paid an up-front license fee of $[***] to Isis which was satisfied (in full) by the issue to Isis of [***] ordinary shares in Atlantic's share capital, which were immediately exchanged for [***] ordinary shares in Atlantic Healthcare's share capital pursuant to the terms of the Subscription and Share Exchange Agreement; *provided, however,*

(a) if at any time during the Anti-Dilution Protection Period (as defined in the Subscription and Share Exchange Agreement) Atlantic Healthcare issues any shares in the capital of Atlantic Healthcare to current shareholders (determined by reference to the date of the Original Agreement) at a subscription price per share of less than £[***], then Isis shall have the right to subscribe for additional AH Shares (as defined in the Subscription and Share Exchange Agreement) at [***] in the share capital of Atlantic Healthcare (for which purpose all shares in Atlantic Healthcare previously issued to Isis pursuant to the Original Agreement shall be deemed held by Isis, irrespective of whether Isis remains the registered holder thereof) had such new shares so issued to existing shareholders [***], as further provided for in the Subscription and Share Exchange Agreement; and

(b) if at any time during the Anti-Dilution Protection Period Atlantic Healthcare issues any shares in the capital of Atlantic Healthcare to [***] (as defined in the Subscription and Share Exchange Agreement) and/or [***] (as defined in the Subscription and Share Exchange Agreement) beyond [***] shares on terms not offered to other shareholders (including Isis), then Isis will have the right to participate on the same terms as [***] (as the case may be) so as to maintain its pro-rata shareholding in Atlantic Healthcare (for which purpose all shares in Atlantic Healthcare previously issued to Isis pursuant to the Original Agreement shall be deemed held by Isis, irrespective of whether Isis remains the registered holder thereof) as further provided for in the Subscription and Share Exchange Agreement.

6.1.2 In no event will Atlantic issue shares to Isis that exceed the Equity Cap.

Section 6.2 **Milestone Payments by Atlantic.**

6.2.1 Atlantic will pay to Isis the relevant milestone payment in cash or in an equivalent amount of Atlantic Equity Securities (subject to the written consent of Atlantic Healthcare Limited and in accordance with the terms of the Subscription and Share Exchange Agreement), at Atlantic's sole discretion, not more than 60 days after achievement by Atlantic, its Affiliates or a sublicensee, of each of the applicable events, as follows:

Event	Payment*
[***]	US $ [***]
[***]	US $ [***]

* In respect of the above payments, Atlantic will be entitled to a single $[***] credit that may be applied to the first [***]% of each milestone payment due under this Section 6.2.1 until such credit is exhausted. For example only, if Atlantic achieves the [***] milestone for an Alicaforsen Product for an indication other than [***], Atlantic may apply the $[***] credit toward the first [***]% of the applicable $[***] milestone payment (*i.e.*, [***]% of $[***] = $[***]), such that after the credit is applied Atlantic will owe Isis a total milestone payment of $[***], and will have a remaining credit of $[***] (*i.e.*, $[***] - $[***] = $[***]) to apply to the first [***]% of another milestone payment under this Agreement.

6.2.2 Notwithstanding the foregoing, in no event will Atlantic issue Atlantic Equity Securities to Isis that exceed the Equity Cap. To the extent any milestone payment of Atlantic Equity Securities will cause Isis' aggregate equity ownership in Atlantic to exceed the Equity Cap, Atlantic will issue to Isis only the number of shares that will maintain such Equity Cap, and will pay Isis the remainder of such milestone payment in cash. For purposes of this Section 6.2, the term "***Atlantic Equity Securities***" means (a) if Atlantic has a class of stock (x) registered under Section 12(b) or 12(g) of the Securities Exchange Act of 1934 and that is publicly traded on a major US exchange such as the NYSE or NASDAQ, or (y) traded on a major European exchange such as Deutsche Börse or the London Stock Exchange, such publicly traded common stock of Atlantic, the value of which will be determined [***]% by the average closing price for the 15 trading days immediately preceding the date the particular milestone event referenced in this Section 6.2 is achieved; or (b) if Atlantic does not have a class of publicly traded stock, the equity securities of Atlantic issued in its most recent venture capital financing occurring prior to the date the particular milestone event referenced in this Section 6.2 is achieved, which will be issued to Isis at the same price per share and with the same rights, preferences and privileges as provided to the other investors in such financing.

Section 6.3 **Sublicense Revenue.**

6.3.1 In the event that Atlantic enters into a Sublicense, Atlantic will pay Isis [***]% of the Sublicense Revenue (which does not include payments based on commercial sales of an Alicaforsen Product, including royalties or profit-sharing) from such sublicensing of any Alicaforsen Product by Atlantic or its Affiliates.

6.3.2 Any payment to Isis for its portion of Sublicense Revenue due under this Section 6.3 will be due within 30 days of Atlantic receiving such Sublicense Revenue.

Section 6.4 **Royalty Payments by Atlantic.**

6.4.1 For any Alicaforsen Product sold by Atlantic or its Affiliates, in consideration of Isis' collaborative efforts and the licenses granted hereunder, Atlantic will pay Isis royalties on Net Sales of each Alicaforsen Product in accordance with the following table:

Cumulative Net Sales	Royalty Rate
Less than US $[***]	[***]%
US $[***] to US $[***]	[***]%
Above US $[***]	[***]%

6.4.2 For any Alicaforsen Products sold pursuant to a Sublicense, in consideration of Isis' collaborative efforts and the licenses granted hereunder, Atlantic will pay Isis royalties on Net Sales as follows:

6.4.2.1 For Alicaforsen Products sold for [***] indication, Atlantic will pay Isis royalties on Net Sales of each Alicaforsen Product equal to the greater of (i) [***]% of the royalty Atlantic is entitled to receive under such Sublicense, or (ii) [***]% of Net Sales; and

6.4.2.2 For an Alicaforsen Product that is not indicated for [***], Atlantic will pay Isis royalties on Net Sales of each Alicaforsen Product as follows:

(a) If the royalty to Atlantic is less than or equal to [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Alicaforsen Product;

(b) If the royalty to Atlantic is greater than [***]% but less than [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Alicaforsen Product; or

(c) If the royalty to Atlantic is equal to or greater than [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Alicaforsen Product.

6.4.3 Isis will be responsible for payment of any Third Party royalty obligations related to an Alicaforsen Product that exist as of the Effective Date ("***Existing Royalties***"), including Existing Royalties due under the agreement with [***] dated [***]. Atlantic will be responsible for all other Third Party royalties, fees and milestones that may arise related to the development or commercialization of Alicaforsen Products.

Section 6.5 **Term; Timing of Royalty Payments.** Atlantic's obligation to pay royalties on each Alicaforsen Product will expire on a country-by-country basis upon the later of: (i) [***] years from the date of First Commercial Sale of such Alicaforsen Product in such country of sale, or (ii) the expiration of the last to expire Valid Claim of Alicaforsen Patents and ICAM-1 Specific Patents covering the making, using, or selling of such Alicaforsen Product in the country of sale, or (iii) the expiration of the last to expire Valid Composition of Matter Claim within Alicaforsen Patents or ICAM-1 Specific Patents in the country of manufacture of that Alicaforsen Product. The royalties due under Section 6.4 will become due and payable: (i) within 30 days of each respective Royalty Due Date with respect to Net Sales received by Atlantic or its Affiliates, and (ii) with respect to royalties due under Sublicenses, within 30 days of Atlantic itself receiving the royalty payments due from its sublicensees. In each case royalties will be calculated in respect of the Net Sales in the calendar quarter immediately preceding the applicable Royalty Due Date.

Section 6.6 **Payment Method.** Any amounts due to Isis under this Agreement will be paid in U.S. dollars, by wire transfer in immediately available funds to an account designated by Isis. Any payments or portions thereof due hereunder which are not paid on the date such payments are due under this Agreement and the payment is not in dispute between the Parties, or if disputed the dispute has not been resolved, will bear interest at a rate equal to the prime rate as published in *The Wall Street Journal*, Eastern Edition, on the first day of each calendar quarter in which such payments are overdue, plus 1% calculated on the number of days such payment is delinquent, compounded monthly.

Section 6.7 **Currency; Foreign Payments.** If any currency conversion will be required in connection with any payment hereunder, such conversion will be made by using the exchange rate for the purchase of U.S. dollars as published in *The Wall Street Journal*, Eastern Edition, on the last business day of the calendar quarter to which such payments relate. If at any time legal restrictions prevent the prompt remittance of any payments in any jurisdiction, Atlantic may notify Isis and make such payments by depositing the amount thereof in local currency in a bank account or other depository in such country in the name of Isis or its designee, and Atlantic will have no further obligations under this Agreement with respect thereto. All payments under this Agreement shall be made free and clear and without any set off, deduction, withholding or deferment in respect of any taxes unless required by law or practice of any relevant governmental authority. The Parties shall co-operate to minimize any deduction or withholding in relation to any payments pursuant to this Agreement.

Section 6.8 **Records Retention; Audit.**

6.8.1 **Record Retention.** Atlantic will maintain (and will ensure that its Affiliates and sublicensees will maintain) complete and accurate books, records and accounts that fairly reflect Net Sales with respect to each Alicaforsen Product, in each case in sufficient detail to confirm the accuracy of any payments required hereunder and in accordance with IFRS, which books, records and accounts will be retained by Atlantic, its Affiliates or sublicensees (as applicable) for the later of (i) 5 years after the end of the period to which such books, records and accounts pertain, and (ii) the expiration of the applicable tax statute of limitations (or any extensions thereof), or for such longer period as may be required by Applicable Law.

6.8.2 **Audit.** Isis will have the right to have an independent certified public accounting firm of nationally recognized standing, reasonably acceptable to Atlantic, have access during normal business hours, and upon reasonable prior written notice, to Atlantic's records (and its Affiliates and sublicensees) as may be reasonably necessary to verify the accuracy of Net Sales, Sublicense Revenue, as applicable, for any calendar quarter or calendar year ending not more than [***] months prior to the date of such request; *provided*, *however*, that Isis will not have the right to conduct more than one such audit in any Calendar Year except as provided below. The accounting firm will enter into appropriate obligations with Atlantic to treat all information it receives during its inspection as confidential. The accounting firm shall disclose to Isis only whether the reported Net Sales and Sublicense Revenue are correct and details of any discrepancies but no other information shall be disclosed to Isis. Isis will bear the cost of such audit unless the audit reveals a variance of more than [***]% from the reported results, in which case Atlantic will bear the cost of the audit.

6.8.3 **Payment of Additional Amounts.** If, based on the results of such audit, additional payments are owed by either party to the other under this Agreement, the party due to make a payment will make such additional payments, with interest as set forth in Section 6.6, within 30 days after the date on which such accounting firm's written report is delivered to such Party.

6.8.4 Confidentiality. Isis will treat the financial information reported to it under Section 6.8.2 in accordance with the confidentiality provisions of Article 8; *provided, however,* that Isis may provide Third Parties to which Isis owes Existing Royalties on Alicaforsen Products such information if it exercises its audit rights concerning the Alicaforsen Products against Isis and provided such Third Party is bound to keep such information confidential.

Section 6.9 **Isis Payment to Atlantic.**

6.9.1 **Up-Front Payment by Isis.** In consideration for the Reverted Rights, Isis hereby provides Atlantic with a single US$[***] credit that may be applied to the purchase of Alicaforsen API under Section 3.6.2 above.

ARTICLE 7 -
PRESS RELEASES & PUBLICATIONS

Section 7.1 **Press Releases**

7.1.1 Press Releases - Generally. Each provision of this Section 7.1.1 is subject to Section 7.1.2 below. Press releases or other similar public communication by either Party relating to this Agreement, will be approved in advance by the other Party, which approval will not be unreasonably withheld or delayed, except (i) disclosures made by Isis related to products covered by the Reverted Rights, or (ii) for those communications required by Applicable Law, which are Authorized Disclosures or disclosures of information for which consent has previously been obtained, and information of a similar nature to that which has been previously disclosed publicly with respect to this Agreement, each of which will not require advance approval, but will be provided to the other Party as soon as practicable after the release or communication thereof.

7.1.2 Press Releases — Product Safety/Efficacy. Each Party will immediately notify (and, if possible, provide as much advance notice as possible to) the other of any event materially related to Alicaforsen Products (including any regulatory approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event, and Isis agrees to provide Atlantic with at least 3 days advance notice of Isis' intention to publicly disclose any adverse safety information related to a Follow-On Product. Notwithstanding Section 7.1.1 above, any press release or other similar public communication by either Party related an Alicaforsen Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least 72 hours in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

Section 7.2 **Publications.** Each provision of this Section 7.2 is subject to Section 7.1.2 above. At least [***] days prior to a Party's submission of any material related to the research or development activities hereunder for publication or presentation, the publishing

Party will provide to the other Party with a draft of such material for its review and comment. The non-publishing Party will provide any comments to the publishing Party within [***] days of receipt of such materials. Except for disclosures made by Isis related to products covered by the Reverted Rights, no publication or presentation with respect to the research or development activities hereunder will be made unless and until the non-publishing Party's comments on the proposed publication or presentation have been discussed by the Parties. If requested in writing by the non-publishing Party, the publishing Party will withhold material from submission for publication or presentation for a reasonable time to allow for the filing of a patent application.

ARTICLE 8 -
CONFIDENTIALITY

Section 8.1 **Disclosure and Use Restriction.** Except pursuant to an Authorized Disclosure, the Parties agree that, for the Term and for five years thereafter, each Party will keep completely confidential and will not publish, submit for publication or otherwise disclose, and will not use for any purpose except for the purposes contemplated by this Agreement, any Confidential Information received from the other Party.

ARTICLE 9 -
INTELLECTUAL PROPERTY

Section 9.1 **Prosecution of Patents.**

9.1.1 Solely Owned Patents. With the exception of the Alicaforsen Patents and the ICAM-1 Specific Patents, which are addressed in Section 9.1.2, each Party will have the sole right, at its cost and expense and at its sole discretion, to obtain, prosecute, maintain and enforce throughout the world any Patents solely owned or Controlled by such Party.

9.1.2 Alicaforsen Patents and ICAM-1 Specific Patents. Subject to Section 9.1.4 below, Isis will have the sole obligation at its expense, to obtain, prosecute and maintain the Alicaforsen Patents and the ICAM-1 Specific Patents in such countries as Isis is prosecuting such Patents on the Restatement Date using Commercially Reasonable Efforts. For clarity, Atlantic will not have the right to review or comment on any applications or registrations to be filed by Isis under this Section 9.1.2, and Isis may cease prosecuting or maintaining particular applications or patents in the Alicaforsen Patents and ICAM-1 Specific Patents in selected jurisdictions, if Isis determines that it is not commercially reasonable to continue such efforts (in which case the terms of Section 9.1.4 will apply).

9.1.3 [Not used]

9.1.4 Discontinued Patents. If under Section 9.1.2 Isis elects to discontinue prosecution or maintenance of any particular applications or patents in the Alicaforsen Patents or the ICAM-1 Specific Patents (if applicable), as the case may be, in a selected jurisdiction, Isis will give thirty (30) days advance written notice to Atlantic of any decision to cease preparation, filing, prosecution and maintenance of that Patent right (a ***"Discontinued Patent"***). In such case, Atlantic may elect at its sole discretion to continue preparation, filing, prosecution or maintenance of the Discontinued Patent in the select jurisdiction at its sole expense and thereafter Atlantic will own any such patent application and patents maturing therefrom and be

solely responsible for all costs. Isis will execute such documents and perform such acts as may be reasonably necessary for Atlantic to continue prosecution or maintenance of the applicable Discontinued Patent including assigning ownership of such Patent or application. Should Atlantic elect to continue preparation, filing, prosecution and maintenance of Discontinued Patents which are Alicaforsen Patents or ICAM-1 Specific Patents, such Patents will no longer be deemed to be Alicaforsen Patents or ICAM-1 Specific Patents for the purposes of this Agreement. Notwithstanding the foregoing, Atlantic's right to continue the preparation, filing, prosecution and maintenance of a Discontinued Patent that is an ICAM-Specific Patent is limited solely to the extent such Patent claims ICAM-1.

9.1.5 Cooperation. Each Party will cooperate reasonably in the preparation, filing, prosecution, and maintenance of the Alicaforsen Patents and the ICAM-1 Specific Patents (if applicable), and the other Party's Patents which cover an Alicaforsen Product. Such cooperation includes

(a) promptly executing all papers and instruments and requiring employees to execute such papers and instruments as reasonable and appropriate so as to enable such other Party, to file, prosecute, and maintain its Patents in any country; and (b) promptly informing such other Party of matters that may affect the preparation, filing, prosecution, or maintenance of any such Patents.

9.1.6 Patent Term Extensions. The Parties agree to cooperate in an effort to avoid loss of any of the Patents forming part of Alicaforsen Patents or ICAM-1 Specific Patents including by executing any documents as may be reasonably required. In particular, the Parties shall cooperate with each other in obtaining patent term extension or restoration or supplemental protection certificate ("***Patent Term Extensions***") or their equivalents in any country and region where applicable. In particular but without limiting the foregoing Isis shall provide reasonable assistance to Atlantic, including by executing any required documents and providing any relevant patent information to Atlantic, so that Atlantic, as Regulatory Approval applicant, may deal with the applicable Regulatory Authority in connection with obtaining such Patent Term Extension.

Section 9.2 **Enforcement of Patents**

9.2.1 Rights and Procedures. If Isis or Atlantic determines that any Patent licensed hereunder is being infringed by a Third Party's activities and that such infringement could affect the exercise by the Parties of their respective rights and obligations under this Agreement, it will promptly notify the other Party in writing. Except for the Alicaforsen Patents and the ICAM-1 Specific Patents which are discussed below, the Party controlling the Patent(s) which are allegedly being infringed will have the sole right and obligation to remove such infringement.

(a) Alicaforsen Patents and ICAM-1 Specific Patents. With respect to the Alicaforsen Patents and the ICAM-1 Specific Patents (if applicable and solely to the extent infringed by a Third Party with a product targeting ICAM-1), Atlantic will have the first right, but not the obligation, at Atlantic's expense, to remove such infringement. In the event that Atlantic fails to take commercially appropriate steps to remove any such infringement within 90 days following notice of such infringement, or earlier notifies Isis in writing of its intent not to take such steps, and such infringement is likely to have a material adverse effect on

the Alicaforsen Product, so long as the infringement is not taking place in a Major Market and so long as Atlantic does not inform Isis that Atlantic considers, in good faith, that to take such proceeds would (x) be prejudicial to its litigation strategy in a Major Market and (y) be commercially unreasonable under the circumstances, (i) Isis will have the right to do so at its expense, (ii) Atlantic will have the right, at its own expense, to be represented in any such action, and (iii) the exclusive license(s) granted under Article 2 that pertain to such Alicaforsen Patent or ICAM-1 Specific Patent (if applicable), will automatically convert into nonexclusive licenses. Isis will have the right, at Isis' own expense, to remove infringement of the Alicaforsen Patents or ICAM-1 Specific Patents (if applicable) (i) if Isis is unilaterally developing and commercializing an Alicaforsen Product pursuant to Section 11.2, (ii) with respect to any products covered by the Reverted Rights, or (iii) if a Third Party is infringing the ICAM-1 Specific Patents with any product that does not target ICAM-1.

(b) Cooperation. The Party not enforcing the applicable Patent will provide reasonable assistance to the other Party (at the enforcing Party's expense), including providing access to relevant documents and other evidence, making its employees available at reasonable business hours, and joining the action to the extent necessary to allow the enforcing Party to maintain the action. If Isis requests that Atlantic take action to remove infringement of an Alicaforsen Patent or ICAM-1 Specific Patent (if applicable) to the extent infringed by a Third Party with a product targeting ICAM-1, and Atlantic believes it is not commercially appropriate to take such actions, the Parties will meet and discuss in good faith such circumstances and seek to reach agreement on what appropriate steps to take to cause such infringement to end in a commercially appropriate manner.

9.2.2 Recovery. Any amounts recovered by Atlantic in connection with or as a result of any action contemplated by Section 9.2.1(a), whether by settlement or judgment, will be used to reimburse the Parties for their reasonable costs and expenses in making such recovery (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses), with any remainder in excess of the reasonable costs and expenses in making such recovery will be treated as Net Sales of an Alicaforsen Product and royalties will be due in respect of such Net Sales pursuant to this Agreement. Isis will retain all amounts it recovers enforcing the Alicaforsen Patents and the ICAM-1 Specific Patents.

ARTICLE 10 - TERM AND TERMINATION

Section 10.1 **Term.** The term of this Agreement (the "***Term***") commences upon the Restatement Date and, unless earlier terminated in accordance with the provisions of this Article 10, will continue until the expiration of all obligations to pay royalties on all Alicaforsen Products to Isis.

Section 10.2 **Rights in Bankruptcy or Insolvency** If either Party becomes insolvent, files a petition in bankruptcy, has such a petition filed against it, determines to file a petition in bankruptcy, or receives notice of a Third Party's intention to file an involuntary petition in bankruptcy, such Party immediately shall notify the other Party in writing. In addition to any other remedies available at law or in equity, the other Party (i.e., the non-bankrupt Party) may immediately terminate this Agreement, in whole or in part as the terminating Party may

determine, upon learning of any of the foregoing events; *provided, however*, that the financial terms set forth in Article 6 above will remain in tact and will survive any such termination. The terminating Party shall provide to the other Party a written notice regarding the extent of termination. If a Party seeks (the "***Filing Party***") to be or is involuntarily placed under the protection of the "*Bankruptcy Code*" (i.e., Title 11, U.S. Code) or its equivalent outside the USA, and the trustee in bankruptcy, or the Filing Party as a debtor-in-possession, rejects this Agreement, then the other Party (the "***Non-Filing Party***") hereby elects, under Section 365(n) of the Bankruptcy Code, to retain all licenses of rights to "intellectual property" (as defined under such Bankruptcy Code) granted to it under this Agreement, to the extent permitted by law. As of the commencement of a bankruptcy proceeding by or against the Filing Party, the Non-Filing Party is entitled to a complete duplicate of all embodiments of "intellectual property" licensed to it hereunder. To the extent such embodiments are not already in the Non-Filing Party's possession as of the commencement of a bankruptcy, the Filing Party (or the trustee in bankruptcy) shall deliver such embodiments to the Non-Filing Party (i) upon any such commencement of a bankruptcy proceeding, unless the Filing Party elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i), then upon a rejection of this Agreement (or the equivalent) by or on behalf of the Filing Party.

Section 10.3 **Material Breach.** Failure by a Party to comply with any of its material obligations contained herein will entitle the Party not in default to give to the defaulting Party notice specifying the nature of the material breach, requiring the defaulting Party to make good or otherwise cure such default, and stating its intention to invoke the provisions of Section 14.4 if such default is not cured. If such default is not cured within 90 days after the receipt of such notice (or, if such default cannot be cured within such 90-day period, if the Party in default does not commence actions to cure such default within such period and thereafter diligently continue such actions), the Party not in default will be entitled, without prejudice to any of its other rights conferred on it by this Agreement, to invoke the provisions of Section 14.4; *provided*, *however*, that in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be stayed until such time as the dispute is resolved pursuant to Section 14.4 hereof.

Section 10.4 **Consequences of Expiration or Termination.**

10.4.1 Licenses. Upon expiration of the Term or upon termination of this Agreement in its entirety by either Party pursuant to Section 10.3, or by Isis pursuant to Section 10.2 and upon payment of all amounts owed pursuant to this Agreement, the licenses granted by Isis to Atlantic hereunder will terminate.

10.4.2 Return of Information and Materials. Upon early termination of this Agreement in its entirety by either Party pursuant to Section 10.3, or by Isis pursuant to Section 10.2, Atlantic will return all data, files, records and other materials in its possession or control relating to or containing or comprising Isis' Confidential Information and, in each case (except one copy of which may be retained for archival purposes).

Section 10.5 **Accrued Rights; Surviving Obligations.**

10.5.1 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.

10.5.2 Survival. Articles 7, 8, 10, 11, 12, and 14, Section 1.2, and Section 6.8 of this Agreement will survive expiration or termination of this Agreement for any reason.

ARTICLE 11
DISCONTINUED DEVELOPMENT BY ATLANTIC

Section 11.1 **Discontinuances.** In the event of a Discontinuance, Isis will have a reversion right as further described in Section 11.2.

Section 11.2 **Reversion Rights.** Following the occurrence of a Discontinuance, Isis may elect to continue to develop any Alicaforsen Product that is the subject of such Discontinuance by notice in writing to Atlantic (an "***Election Notice***") that Isis is exercising its rights under this Section 11.2, in which case this Agreement will terminate (subject to the survival provisions set forth in Section 10.5.2). Upon receipt of an Election Notice, Atlantic will (i) grant to Isis a sublicensable, worldwide license or sublicense, as the case may be, to all Patents controlled by Atlantic solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import the Alicaforsen Product and (ii) transfer to Isis, for Isis' unlimited use, any data, results, regulatory information and files in the possession of Atlantic as of the date of the Election Notice that relate to the Alicaforsen Product, subject to the negotiation in good faith of a reasonable royalty payable to Atlantic that represents the value of the items transferred to Isis.

ARTICLE 12 -

INDEMNIFICATION AND INSURANCE

Section 12.1 **Indemnification of Isis.** Atlantic will indemnify Isis and its Affiliates, and each of their respective directors, officers, employees and agents, and defend and hold each of them harmless, from and against any and all losses, damages, liabilities, costs and expenses (including reasonable attorneys' fees and expenses) to the extent arising from or occurring as a result of any and all liability suits, investigations, claims or demands by a Third Party (collectively, "***Losses***") arising from or occurring as a result of or in connection with (a) the breach of any of Atlantic's representations, warranties, or covenants contained in Article 13 below, or (b) whether or not negligence is found or alleged, the manufacture (except to the extent attributable to Isis' negligence), use, handling, storage, sale or other disposition of an Alicaforsen Product or other compound that is developed or sold by Atlantic, its Affiliates, agents or sublicensees, except to the extent Isis has an obligation to indemnify Atlantic under Section 12.2 below.

Section 12.2 **Indemnification of Atlantic.** Isis will indemnify Atlantic, its Affiliates, and its sublicensees, and each of their respective directors, officers, employees and agents, and defend and hold each of them harmless, from and against any and all Losses arising from or occurring as a result of or in connection with (a) the breach of any of Isis' representations, warranties, or covenants contained in Article 13 below, or (b) whether or not negligence is found or alleged, the manufacture, use, handling, storage, sale or other disposition of a compound that is developed or sold by Isis, its Affiliates, agents or sublicensees, except to the extent Atlantic has an obligation to indemnify Isis under Section 12.1 above.

Section 12.3 **Insurance.** Each Party will have and maintain such types and amounts of liability insurance as is reasonable and customary in the industry generally for parties similarly situated, and will upon request provide the other with a certificate of insurance. Each Party will promptly notify the other of any material change in insurance coverage or lapse in coverage in that regard.

Section 12.4 **Liability.** Neither Party shall be liable to the other in contract, tort, negligence, breach of statutory duty or otherwise for any loss, damage, costs or expenses of any nature whatsoever incurred or suffered by the other or its Affiliates:

12.4.1 of a direct nature where the same is a loss of turnover, profits, business or goodwill; or

12.4.2 of an indirect or consequential or punitive nature, including any indirect or consequential economic loss or other indirect or consequential loss of turnover, profits, loss of enterprise value, business or goodwill or otherwise.

ARTICLE 13 -
REPRESENTATIONS AND WARRANTIES

Section 13.1 **Representations, Warranties and Covenants.** Each Party hereby represents, warrants and covenants to the other Party as of the Restatement Date as follows:

Section 13.2 **Corporate Authority.** Such Party (a) has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and (b) has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder. This Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity.

Section 13.3 **Consents, Approvals, etc.** All necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained.

Section 13.4 **Conflicts.** The execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the articles of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound.

Section 13.5 **Intellectual Property**. To each Party's knowledge, as of the Effective Date, no additional Third Party licenses are required to develop, use and sell the enema formulation of Alicaforsen.

Section 13.6 **Isis Representations, Warranties, and Covenants**. Isis hereby represents, warrants and covenants to Atlantic as of the Effective Date as follows:

13.6.1 **IP Ownership**. Isis has the sufficient legal and/or beneficial title and ownership of the Alicaforsen Patents and the ICAM-1 Specific Patents as is necessary to fulfill its obligations under this Agreement and to grant the licenses (or sublicenses as the case may be) to Atlantic pursuant to this Agreement; Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, licensed, transferred, conveyed or otherwise encumbered its right, title or interest in or to the Isis Data ("***Isis Background Know How***") or the Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder (including by granting any covenant not to sue with respect thereto) (the Isis Background Know How and such Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder together being the "***Isis Background IP***"). To the best of Isis' knowledge, the conception, development and reduction to practice of the Isis Background IP existing as of the Effective Date have not constituted or involved the misappropriation of trade secrets or other rights or property of any Third Party; and

13.6.2 **Patent Maintenance.** True, complete and correct copies of the complete file wrapper and other material correspondence with any patent office relating to the prosecution, validity and enforceability of the Patents within the Alicaforsen Patents and the ICAM-1 Specific Patents existing at the Effective Date have been provided to or made available to Atlantic prior to the Effective Date and, to the best of Isis' knowledge, there is no material reason why any of such Patents are invalid. In respect of the pending patent applications included within such Patents, Isis has presented all relevant prior art of which it and the inventors are aware to the relevant patent examiners at the relevant patent offices; and

13.6.3 **Patent Prosecution.** The Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder that are applications at the Effective Date are being diligently procured from the respective patent offices and the Patents within such Patents licensed hereunder that are granted at the Effective Date have been maintained properly and correctly and all applicable fees have been paid on or before the due date for payment; and

13.6.4 **Third Party Actions.** To the best of Isis' knowledge, no actions, suits, claims, disputes, or proceedings concerning the Alicaforsen Patents or the ICAM-1 Specific Patents licensed hereunder or the Alicaforsen Product are currently pending or are threatened in writing, that if determined adversely to Isis would have a material adverse effect on the Alicaforsen Product or would impair Isis' ability to perform its obligations under this Agreement.

13.6.5 **Alicaforsen.** As of the Effective Date, Isis does not Control any Patents other than the Alicaforsen Patents and the ICAM-1 Specific Patents that would be necessary to develop or commercialize Alicaforsen Products or to manufacture Alicaforsen Product or Alicaforsen API other than the Patents within Excluded Isis IP and, to the best of Isis' knowledge, Isis does not Control any know-how that would be necessary to develop or commercialize Alicaforsen Products other than the Isis Data and know-how transferred to Atlantic under Section 2.2.1.

Section 13.7 **Enabled CMOs.** Isis hereby represents and warrants, as of the Restatement Date, that each of Avecia Biotechnology, Inc., Agilent Technologies, Inc., and Girindus America Inc. is an Enabled CMO.

Section 13.8 **Atlantic Representations, Warranties, and Covenants.** Atlantic hereby represents, warrants and covenants to Isis that:

13.8.1 **Capabilities.** As of the Effective Date, Atlantic has the requisite personnel, expertise, experience and skill to perform its obligations under this Agreement; Atlantic's sales representatives will perform in a professional, timely, competent and efficient manner; and Atlantic, its

Affiliates, and its sublicensees will at all times comply with all Applicable Laws.

13.8.2 Sublicenses. As of the Restatement Date, Atlantic has not granted any sublicenses (including Sublicenses) under the Original Agreement, *except* that certain Development and License Agreement with Sigma Pharmaceuticals (formerly Orphan Australia Pty. Ltd.) executed on or about December 6, 2007, which is in full compliance with, and remains subject to, the terms and conditions of this Agreement.

13.8.3 Payment Obligations. As of the Restatement Date, no payment obligations have accrued under the Original Agreement that have not been paid by Atlantic to Isis.

Section 13.9 **DISCLAIMER OF WARRANTY.** EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 13, ATLANTIC AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ATLANTIC AND ISIS EACH SPECIFICALLY DISCLAIM ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 14 - MISCELLANEOUS

Section 14.1 **Assignment.** Without the prior written consent of the other Party hereto, neither Party will sell, transfer, assign, delegate, pledge or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder; *provided*, *however,* that (i) either Party hereto may assign or transfer this Agreement or any of its rights or obligations hereunder without the consent of the other Party to (a) any of its Affiliates, or (b) any Third Party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets to which this Agreement relates provided always in the case where Isis is the assigning Party it also transfers title to the Alicaforsen Patents or the ICAM-1 Specific Patents to such Third Party, and if in any such event the Third Party assignee or surviving entity assumes in writing all of the assigning Party's obligations under this Agreement, (ii) Atlantic may assign or transfer this Agreement, without Isis' consent, to Atlantic Healthcare, or (iii) Isis may assign or transfer its rights under Article 6.4 (but no liabilities) to a Third Party in connection with a royalty factoring transaction. Any purported assignment or transfer in violation of this Section 14.1 will be void *ab initio* and of no force or effect.

Section 14.2 **Severability.** If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

Section 14.3 **Governing Law.** This Agreement will be governed by and construed in accordance with the laws of New York, USA without reference to any rules of conflicts of laws.

Section 14.4 **Dispute Resolution.**

14.4.1 General. Any dispute, controversy or claim arising from or related to this Agreement or the breach thereof will first be referred to the attention of the Chief Executive Officer of Atlantic and the Chief Operating Officer of Isis (the "***Executive Officers***") by notice in writing in accordance with the terms of this Agreement. The Executive Officers (or their respective designees) will meet as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim. If any dispute, controversy or claim is not resolved by the designated officers of the Parties (or their designees) within 30 days after such dispute is referred to them, then the Parties agree that such dispute will be referred to mediation, and if the dispute remains unresolved after mediation, either Party will have the right to arbitrate such dispute in accordance with Section 14.4.3; *provided*, *however*, that any dispute relating to the construction or validity of any Patent will not be subject to arbitration.

14.4.2 Mediation. If the Parties pursue mediation proceedings the Parties will attempt to resolve such dispute in accordance with the Commercial Mediation Procedures of the American Arbitration Association ("***AAA***"), before resorting to arbitration in accordance with Section 14.4.3 below. The mediation will be conducted by a single mediator experienced in the business and technology that is the subject of this Agreement. The place of mediation will be in New York, NY, USA. Either Party may apply to the mediator or to a court for interim injunctive relief until the mediation decision is rendered or the dispute, controversy or claim is otherwise resolved.

14.4.3 Arbitration. If the Parties do not fully settle any dispute, controversy or claim pursuant to Section 14.4.1 or 14.4.2 and a Party wishes to pursue the matter further, each such dispute, controversy or claim will be finally resolved by binding arbitration in accordance with the Commercial Arbitration Rules of the AAA, and judgment on the arbitration award may be entered in any court having jurisdiction thereof. The arbitration will be conducted by a single arbitrator agreeable by the Parties, if the Parties cannot agree upon an arbitrator, the arbitrator will be appointed by the AAA. No individual will be appointed to arbitrate a dispute pursuant to this Agreement unless he or she agrees in writing to be bound by the provisions of this Section 14.4. The place of arbitration will be New York, NY, USA. Either Party may apply to the arbitrator for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved.

14.4.4 Disputes Regarding Material Breach. If the Parties are in dispute as to whether one party is in material breach of this Agreement, then the mediator or arbitrators will first determine if material breach has in fact occurred, and if so, will grant the defaulting Party the cure period provided pursuant to Section 10.3. If the material breach is not cured within the time period provided pursuant to Section 10.3, the mediation or arbitration will continue and the mediator or arbitrators will, as part of the same mediation or arbitration, award actual direct damages to the non-defaulting Party.

14.4.5 Costs and Expenses. Except as expressly provided herein, each Party will bear its own costs and expenses and attorneys' fees and an equal share of the mediator's and/or arbitrators' and any administrative fees of mediation and arbitration. Notwithstanding the foregoing, in the case of arbitration, if a Party has been found to be in material breach of this Agreement, the defaulting Party will be responsible for both Parties' Third Party costs and expenses (including the costs of the arbitrators and any administrative fees of arbitration) and the reasonable attorneys' fees of the non-defaulting Party; *provided, however*, that the total amount of such fees and expenses the defaulting Party is required to reimburse the non-defaulting Party cannot exceed the total amount of monetary damages awarded to the non-defaulting Party as a result of such material breach.

14.4.6 Procedure. Except to the extent necessary to confirm an award or as may be required by law, neither a Party, a mediator, nor an arbitrator may disclose the existence, content, or results of a mediation or an arbitration without the prior written consent of both Parties. In no event will arbitration be initiated after the date when commencement of a legal or equitable proceeding based on the dispute, controversy or claim would be barred by the applicable New York statute of limitations.

14.4.7 Speedy Resolution. The Parties intend, and will take all reasonable action as is necessary or desirable to ensure, that there be a speedy resolution to any dispute which becomes the subject of mediation or arbitration, and the mediator and arbitrators will conduct the mediation or arbitration so as to resolve the dispute as expeditiously as possible.

14.4.8 Awards. In any mediation, a decision or opinion issued by the mediator regarding the dispute between the Parties is non-binding. The arbitrators may award monetary damages and injunctive relief, but may not order the granting or termination of licenses or assign rights to an Alicaforsen Product to either of the Parties. Monetary damages will be in the form of off-set royalties or otherwise, to account for the damages to the non-defaulting Party from the breach, and to account for the defaulting Party's contribution to the Alicaforsen Product in view of the breach. All awards will be in writing and will state reasons. Executed copies of all awards will be delivered by the arbitrators to the Parties as soon as is reasonably possible. All awards of the arbitrators will be final and binding on the Parties, and there will be no appeal of any such award whatsoever. The Parties undertake to satisfy any award without delay.

Section 14.5 **Notices.** All notices or other communications that are required or permitted hereunder will be in writing and delivered personally with acknowledgement of receipt, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier as provided herein), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to Atlantic, to:

Atlantic Pharmaceuticals Limited
MoFo Notices Limited
7th Floor
CityPoint
One Ropemaker Street
London EC2Y 9AW
Attention: Chief Executive Officer
Facsimile: +44 (0) 20 7496 8500

If to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008
Attention: Chief Operating Officer and CFO
Facsimile: +1 (760) 603-4650

with a copy to:

Attention: General Counsel
Facsimile: +1 (760) 268-4922

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication will be deemed to have been given (i) when delivered, if personally delivered or sent by facsimile on a Business Day, (ii) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (iii) on the third business day following the date of mailing, if sent by mail. It is understood and agreed that this Section 14.5 is not intended to govern the day-to-day business communications necessary between the Parties in performing their duties, in due course, under the terms of this Agreement.

Section 14.6 **Entire Agreement; Modifications.** This Agreement (and the Subscription and Share Exchange Agreement) sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof and all prior agreements (including the Original Agreement), understandings, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

Section 14.7 **Relationship of the Parties.** It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

Section 14.8 **Waiver.** Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver will be effective unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. Any such waiver will not be deemed a waiver of any other right or breach hereunder.

Section 14.9 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

Section 14.10 **No Benefit to Third Parties.** The provisions of this Agreement are for the sole benefit of the Parties and their successors and permitted assigns. This Agreement shall not confer any rights or remedies upon any person other than Isis and Atlantic and their respective successors and permitted assigns except as otherwise expressly provided in Section 12. Except as expressly provided in Section 12, no person who is not a party to this Agreement (including any employee, officer, agent, representative or subcontractor of either Party) shall have the right to enforce any terms of this Agreement which expressly or by implication confers a benefit on that person without the prior written agreement of the Parties which agreement must refer to this Section 14.10.

Section 14.11 **Further Assurance.** Each Party will duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary to carry out the provisions and purposes of this Agreement.

Section 14.12 **Force Majeure.** Neither Party shall be responsible to the other for any failure or delay in performing any of its obligations under this Agreement or for other non-performance hereunder if such delay or non-performance is caused by strike, stoppage of labor, lockout or other labor trouble, fire, flood, accident, war, act of terrorism, act of God or of the government of any country or of any local government, or by cause unavoidable or beyond the control of any Party hereto. In such event, the Party affected will use Commercially Reasonable Efforts to resume performance of its obligations.

[SIGNATURES ON FOLLOWING PAGE]

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the Restatement Date.

ATLANTIC PHARMACEUTICALS LIMITED	**ISIS PHARMACEUTICALS, INC.**
Per: */s/ Toby Wilson Waterworth*	Per: */s/ B. Lynne Parshall*
Toby Wilson Waterworth Director	B. Lynne Parshall Chief Operating Officer & CFO

APPENDIX 1

Definitions

"Affiliate" of a Party means any other party that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such Party. For purposes of this definition only, "*control*" and, with correlative meanings, the terms "*controlled by*" and "*under common control with*" will mean the possession, directly or indirectly, of the power to direct the management or policies of a party, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance. Notwithstanding the foregoing, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Isis for the purposes of this Agreement.

"***Agreement***" has the meaning set forth in the Preamble.

"Alicaforsen" means the compound known by the USAN name "*Alicaforsen*," which is also known as ISIS 2302.

"Alicaforsen API" means Alicaforsen in bulk form manufactured in accordance with cGMP for use in an Alicaforsen Product.

"Alicaforsen Patents" means (i) the Patents listed on Appendix 2, and (ii) all Patents issuing from the Patents in (i), and (iii) any other Patent Controlled by Isis during the term of this Agreement which covers the composition, formulation or use of Alicaforsen *but excluding always* the Patents within Excluded Isis IP and the ICAM-1 Specific Patents.

"Alicaforsen Product" means a pharmaceutical preparation comprising Alicaforsen.

"Applicable Law" means all applicable laws, rules, and regulations, including any rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"Atlantic Equity Securities" has the meaning set forth in Section 6.2.2.

"Atlantic Healthcare" means that company incorporated in England and Wales with company registration no. 5878612 whose registered address is Maple House, Birdbrook, Halstead, Essex CO9 4BB.

"Authorized Disclosure" means a disclosure of Confidential Information by the receiving Party to the extent that such disclosure is:

(i) made in response to a valid order of a court of competent jurisdiction; *provided*, *however*, that such receiving Party will first have given notice to such other Party and given such other Party a reasonable opportunity to quash such order and to obtain a protective order requiring that the Confidential Information and documents that

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are the subject of such order be held in confidence by such court or agency or, if disclosed, be used only for the purposes for which the order was issued; and *provided further* that if a disclosure order is not quashed or a protective order is not obtained, the Confidential Information disclosed in response to such court or governmental order will be limited to that information which is legally required to be disclosed in response to such court or governmental order;

(ii) otherwise required to comply with Applicable Laws, including to the extent such disclosure is required in publicly filed financial statements or other public statements under rules governing a stock exchange (e.g., the rules of the United States Securities and Exchange Commission, NASDAQ, NYSE, UKLA or any other stock exchange or which securities of either Party may be listed) *provided*, *however*, to the extent possible bearing in mind such Applicable Laws and subject to the next subsequent sentence of this paragraph, the receiving Party shall provide the other Party with a copy of the proposed text of such statements or disclosure five (5) Business Days in advance of the date on which the disclosure is to be made to enable the other Party to review and provide comments, unless a shorter review time is agreed. If the compliance with an Applicable Law requires filing of this Agreement, the filing Party shall to the extent possible seek confidential treatment of portions of this Agreement from the relevant competent authority and shall provide the other Party with a copy of the proposed filings at least ten (10) Business Days prior to filing for the other Party to review any such proposed filing. Each Party agrees that it will obtain its own legal advice with regard to its compliance with Applicable Laws and will not rely on any statements made by the other receiving Party relating to such laws;

(iii) made by such receiving Party to the Regulatory Authorities as necessary for (a) the development or commercialization of a Alicaforsen Product in a particular country, or (b) as required in connection with any filing, application or request for Regulatory Approval in a particular country and in either case to the extent consistent with the licenses granted under the terms of this Agreement;

(iv) made by the receiving Party, in connection with the performance of this Agreement, to Affiliates sublicensees, licensors, licensees, directors, officers, employees, consultants, representatives or agents, each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Agreement;

(v) made by the receiving Party to existing or potential acquirers; existing or potential pharmaceutical collaborators (to the extent contemplated hereunder); investment bankers; existing or potential investors, merger candidates, partners, venture capital firms or other financial institutions or investors for purposes of obtaining financing; or, bona fide strategic potential partners; each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Agreement; or

(vi) made by the receiving Party to its legal advisers for the purpose of seeking advice.

"Business Day" means 9.00am to 5.00pm local time on any day, other than Saturday, Sunday or any statutory holiday or public holiday in the United States or England and Wales.

"Calendar Year" means each successive period of 12 months commencing on January 1 and ending on December 31.

"***cGMP***" means current Good Manufacturing Practices as specified in ICH Guideline Q7A, the United States Code of Federal Regulations, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"***Commercially Reasonable Efforts***" (i) in respect of Atlantic means efforts and resources commonly used in the biotechnology industry by companies at a similar stage of development for products of similar commercial potential to develop and commercialize a product owned by such a company or to which it has rights, which product is at a similar stage in its development or product life and is of similar market potential to the Alicaforsen Product in question and taking into account the patent and other proprietary position of the product; and (ii) in respect of Isis means efforts and resources commonly used by biotechnology companies of a similar size to Isis based on market capitalization to develop a product owned by such a company or to which it has rights, which product is at a similar stage in its development or product life and is of similar market potential to the Alicaforsen Product in question and taking into account the patent and other proprietary position of the product. If Atlantic is commercializing Alicaforsen in a given Major Market in accordance with the Development Plan, such commercialization will be deemed to be an example of using Commercially Reasonable Efforts; *provided*, *however*, that a failure to so commercialize in such a Major Market will not be dispositive of a failure to use Commercially Reasonable Efforts.

"Committee Members" has the meaning set forth in Section 3.2.

"Confidential Information" means all information and know-how and any tangible embodiments thereof provided by or on behalf of one Party to the other Party either in connection with the discussions and negotiations pertaining to this Agreement or the Original Agreement, or in the course of performing this Agreement or the Original Agreement, including data; knowledge; practices; processes; ideas; research plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the disclosing Party or to its present or future products, sales, suppliers, customers, employees, investors or business.

Exceptions. Notwithstanding the foregoing, information or know-how of a Party will not be deemed Confidential Information for purposes of this Agreement if such information or know-how:

(a) was already known to the receiving Party, other than under an obligation of confidentiality or non-use, at the time of disclosure to such receiving Party;

(b) was generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or was otherwise part of the public domain, at the time of its disclosure to, or, with respect to know-how, discovery or development by, such receiving Party;

(c) became generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or otherwise became part of the public domain, after its disclosure to such receiving Party through no fault of the receiving Party;

(d) was disclosed to such receiving Party, other than under an obligation of confidentiality or non-use, by a Third Party who had no obligation to the disclosing Party not to disclose such information or know-how to others; or

(e) was independently discovered or developed prior to disclosure by such receiving Party, as evidenced by their written records, without the use of Confidential Information belonging to the disclosing Party.

"Control" means, with respect to any Patent or other intellectual property right, possession of the right (whether by ownership, license or otherwise), to assign, or grant a license, sublicense or other right to or under, such Patent or right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party or incurring any additional financial or other obligation to a Third Party except the obligations specifically described in Section 6.7.

"Cumulative Net Sales" means the total cumulative amount of Net Sales calculated separately for each of the Alicaforsen Products, from the first date that each such product was approved for commercialization by a Regulatory Authority.

"***Development Plan***" means a written plan for the development of an Alicaforsen Product which describes the planned activities and timelines including:

a) Pre-clinical studies
b) Formulation development
c) Clinical studies
d) Regulatory activities
e) Manufacturing process development and scale up
f) Pharmacovigilance plans
g) Commercialization plans

The term "Development Plan" includes the Initial Development Plan approved by Isis and Atlantic and attached to this Agreement as Appendix 4.

"Discontinuance" means the occurrence of any one of the following:

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1. Atlantic voluntarily elects to abandon researching, developing and/or commercializing all Alicaforsen Products, as evidenced by a written communication from an authorized officer of Atlantic to Isis; or

2. Atlantic fails to use Commercially Reasonable Efforts and the Quality Standard to develop and commercialize at least one Alicaforsen Product.

"***Discontinued Patent"*** has the meaning set forth in Section 9.1.4.

"***Effective Date***" means March 7, 2007.

"***EMEA"*** means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

"***Enabled CMO***" means a Third Party engaged in the business of contract manufacturing to which Isis has granted a license to certain of Isis' manufacturing intellectual property for the manufacture of oligonucleotides, including Alicaforsen API.

"***Enema Delivery***" means a route of delivery directly into an ostomy or the rectum to achieve a local effect in the gastrointestinal tract or a systemic therapeutic effect.

"Equity Cap" means [***]% of the issued and outstanding share capital of Atlantic (on an as-issued, post financing basis).

"Excluded Isis IP" means all know how and Patents Controlled by Isis on the Effective Date and at any time during the term of the Agreement *other than* (A) Alicaforsen Patents, (B) ICAM-1 Specific Patents, (C) Isis Data, and (D) Isis Manufacturing Know How. For clarity, Excluded Isis IP includes any know how and Patents Controlled by Isis which cover Isis' (i) formulation and delivery technology (save as expressly claimed in the Alicaforsen Patents, ICAM-1 Specific Patents and Isis Manufacturing Know How), (ii) RNAi technologies, (iii) microRNA technologies, and (iv) chemical modifications and motifs, and (v) the Excluded Manufacturing IP.

"Excluded Manufacturing IP" means all Patents and know how (including any and all information directly relating to manufacturing methods (including related analytical methods) of Alicaforsen API) Controlled by Isis on the Effective Date and at any time during the term of the Agreement which claim the manufacturing process by which Isis manufactures Alicaforsen API.

"Existing Royalties" has the meaning set forth in Section 6.4.3.

"FDA" means the United States Food and Drug Administration and any successor agency thereto.

"First Commercial Sale" means the first sale of an Alicaforsen Product by Atlantic, its Affiliates or a sublicensee to a Third Party in a particular country after Regulatory Approval has been obtained.

"***Follow-On Product***" means a pharmaceutical composition, formulation, dosage form, delivery system and presentation discovered and developed by Isis after the Restatement Date that contains a nucleic acid that hybridizes to a nucleic acid molecule encoding ICAM-1 (alone or with other active ingredients) that has a different chemistry than Alicaforsen.

"IBD" means a chronic disorder of the [***], including without limitation, [***] or [***].

"ICAM-1" means intercellular adhesion molecule-1 (also called CD54).

"ICAM-1 Specific Patents" means (i) the Patents listed on Appendix 3 (ii) all Patents issuing therefrom, and (iii) any other Patents Controlled by Isis during the term of this Agreement which cover the composition, formulation or use of Alicaforsen Products, *but excluding always* the Alicaforsen Patents and the Patents within Excluded Isis IP.

"IFRS" means International Financial Reporting Standards established by the International Accounting Standards Board, as amended from time to time.

"***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-Supporting Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND.

"***[***]***" means a route of delivery into the human body by [***] directly into the [***] of a human being.

"***Initiation of a Phase I Clinical Trial"*** means the first visit by the first human patient in a Phase I Clinical Trial during which dosing of an Alicaforsen Product or placebo occurs.

"Initiation of a Pivotal Quality Clinical Trial" means the first visit by the first patient in a Pivotal Quality Clinical Trial during which dosing of an Alicaforsen Product or placebo occurs.

"***Intramuscular Injection***" means an injection directly into muscle of a human being.

"***Intravenous Injection***" means an injection directly into a vein of a human being.

"Isis Background IP" has the meaning set forth in Section 13.6.1.

"Isis Background Know How" has the meaning set forth in Section 13.6.1.

"Isis Data" has the meaning set forth in Section 2.2.1.

"Isis Database" has the meaning set forth in Section 3.3.1.

"Isis Manufacturing Know How" has the meaning set forth in Section 2.2.1.

"JDC" has the meaning set forth in Section 3.2.

"Losses" has the meaning set forth in Section 12.1.

"Major Market" means the [***] and [***].

"NDA" means a New Drug Application filed with the FDA after completion of clinical trials to obtain Regulatory Approval for commercial product in the United States or an equivalent application for regulatory approval in other Major Market countries.

"***NDA Filing***" means the acceptance by the FDA or other Regulatory Authority of the filing of an NDA for the applicable Alicaforsen Product.

"***Net Sales***" means the gross invoiced price charged by Atlantic or its Affiliates or sublicensees, as appropriate, for the sale of an Alicaforsen Product to a Third Party by Atlantic, its Affiliates or its sublicensees, as appropriate, less the following deductions:

(i) Trade and quantity discounts actually granted;

(ii) Credits for returns or allowances;

(iii) Actual uncollectible amounts for Alicaforsen Product where collectibility is determined in accordance with IFRS consistently applied to all of Atlantic's products;

(iv) Freight, shipping insurance and other transportation expenses directly related to the sale of the Alicaforsen Product (if actually borne by Atlantic, its Affiliates or sublicensees without reimbursement from any Third Party);

(v) The amount of any sales tax or other taxes assessed directly on the sale of such Alicaforsen Product which is not refunded; and

(vi) Charge back payments or rebates granted to managed health care organizations or federal, state and local governments, their agencies, purchasers and reimburses.

The transfer of Alicaforsen Product by Atlantic or one of its Affiliates to another Affiliate shall not be considered a sale. Upon the sale or other disposal of Alicaforsen Product for other than monetary consideration , which sales price is either customary or is reasonably expected in the country in which such sale is made, such sale or other disposal shall be deemed to be a sale with the consideration for such sale constituting Net Sales hereunder at the average sales price during the applicable reporting period generally achieved (or as achieved by similar products) for such Alicaforsen Product in the country in which such sale or other disposal occurred when such Alicaforsen Product is sold

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alone and not with other products. Disposal of Alicaforsen Product for or use of Alicaforsen Product in clinical trials or as free samples shall not be deemed a sale under this definition. Such amounts shall be determined from the books and records of Atlantic maintained in accordance with IFRS, consistently applied.

Where Alicaforsen Product contains Alicaforsen and is sold in combination with one or more other active ingredient(s) that are sold either as a fixed dose or as separate doses in a single package for a single price (a "***Combination Product***"), Net Sales will be determined as follows:

(X divided by Y) multiplied by Z

where X is the average sales price during the applicable reporting period generally achieved for the Alicaforsen Product in the country in which such sale or other disposal occurred when such Alicaforsen Product is sold alone and not as a Combination Product; Y is the sum of the average sales price during the applicable reporting period generally achieved in that country, when sold alone, by each product (including the Alicaforsen Product) included in the Combination Product that is sold for the single price; and Z equals the single price at which the Combination Product represented in Y was actually sold. In the event one or more of the products in the Combination Product are not sold separately, the Parties shall confer in good faith to determine a fair market price that shall be equitable for the value of the Alicaforsen Product within the Combination Product.

"***Oral Delivery***" means a route of delivery using a tablet or capsule into the alimentary canal of a human being to achieve a local effect in the gastrointestinal tract or a systemic therapeutic effect.

"Patents" will include (x) all U.S. patents and patent applications, (y) any substitutions, divisions, continuations, reissues, renewals, registrations, confirmations, re-examinations, extensions, supplementary protection certificates and the like, and any provisional applications, of any such patents or patent applications, and (z) any foreign or international equivalent of any of the foregoing.

"Patent Term Extensions" has the meaning set forth in Section 9.1.6.

"***Phase I Clinical Trial"*** means the initial clinical testing of an Alicaforsen Product in humans (first-in-humans study).

"Pivotal Quality Clinical Trial" means a human clinical trial of an Alicaforsen Product designed to be of a size and statistical power to support an NDA Filing alone or in combination with other studies. If it is unclear whether or not a study design will be sufficient to support an NDA Filing (other than by virtue of the uncertainty of safety and efficacy data from that trial) the study will be deemed to be a Pivotal Quality Clinical Trial on the initiation of activities to support an NDA Filing. A Phase III clinical study will be deemed to be a Pivotal Quality Clinical Trial.

"Positive Pouchitis Clinical Trial" means a clinical study of an Alicaforsen Product in humans conducted by Atlantic in accordance with this Agreement that is directed to the treatment of Pouchitis, which meets the study's primary endpoint(s).

"***Pouchitis***" means inflammation of the mucosa, or of the full thickness, of the intestinal wall of an ileal or ileoanal reservoir.

"Quality Standard" means, with respect to research, development, manufacture or commercialization of an Alicaforsen Product, the standard of care, quality, and professional competence commonly used in the biotechnology industry for products of similar commercial potential at a similar stage in its lifecycle.

"Regulatory Approval" means (a) in the United States, approval by the FDA of an NDA, or similar application for marketing approval, and satisfaction of any related applicable FDA registration and notification requirements (if any), and (b) in a Major Market other than the United States, approval by Regulatory Authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA and satisfaction of any related applicable regulatory and notification requirements (if any).

"Regulatory Authority" means any applicable government entities regulating or otherwise exercising authority with respect to the development and commercialization of an Alicaforsen Product.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all Regulatory Approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all clinical studies and tests, including the manufacturing batch records, relating to an Alicaforsen Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files.

"***Reverted Rights***" has the meaning set forth in Section 1.2.1.

"Royalty Due Dates" means the last working days of March, June, September and December of each and every year during which this Agreement remains in full force and effect.

"***Subcutaneous Injection***" means an injection directly into the subcutaneous tissue of the human body between the skin and the muscle of a human being.

"Sublicense" means a sublicense from Atlantic to a Third Party under the Alicaforsen Patents or the ICAM-1 Patents to develop, use, sell, offer for sale, have sold and/or import any Alicaforsen Product.

"Sublicense Revenue" means any consideration that Atlantic receives from a sublicensee in consideration for a grant of any Sublicense, including, but not limited to, license fees, milestone payments, and license maintenance fees, but excluding: (i) royalties on Net Sales of Alicaforsen Products, (ii) payments made in consideration of equity or debt securities of Atlantic at fair market value and (iii) payments specifically committed to reimburse Atlantic for the direct cost of research and development. If Atlantic receives any non-cash Sublicense Revenue, Atlantic will pay Isis, at Isis' election, either (x) a cash payment equal to the fair market value of Isis' appropriate portion of the Sublicense Revenue or (y) the in-kind portion, if practicable, of the Sublicense Revenue. For purposes of calculating Sublicense Revenue, a series of Sublicenses to the same sublicensee or related sublicensees will be aggregated to constitute a single Sublicense.

"***Subscription and Share Exchange Agreement***" has the meaning set forth in Section 1.2.1.

"***Systemic Delivery***" means a route of delivery directly into the bloodstream to reach and affect cells in all areas of the body, which includes by Intravenous Injection, Intramuscular Injection, Subcutaneous Injection and Oral Delivery. "*Systemic Delivery*" does not include [***].

"Term" has the meaning set forth in Section 10.1.

"Third Party" means any party other than Isis or Atlantic or their respective Affiliates.

"Valid Claim" means a claim of a Patent which (i) in the case of any granted, unexpired United States or foreign Patent, shall not have been donated to the public, disclaimed or held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) in the case of any United States or foreign patent application, is being prosecuted in good faith and shall not have been permanently cancelled, withdrawn, or abandoned provided that no more than eight (8) years have passed since the earliest priority date for such application.

"Valid Composition of Matter Claim" means a Valid Claim of a Patent in a given country that covers the structure of the compound comprising the active pharmaceutical ingredient in the Alicaforsen Product as opposed to its process of manufacture, use or method of treatment.

APPENDIX 2

ALICAFORSEN PATENTS

[***]

APPENDIX 3

ICAM-1 SPECIFIC PATENTS

[***]

APPENDIX 4

INITIAL DEVELOPMENT PLAN

[Attached]

[***]

FIRST AMENDMENT TO LOAN AGREEMENT

THIS FIRST AMENDMENT TO LOAN AGREEMENT (this "Amendment") is made and entered into as of September 30, 2009, between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (together with its successors and assigns, "Borrower"), and **RBS ASSET FINANCE, INC.**, a New York corporation (together with its successors and assigns, "Lender").

RECITALS

A. Lender and Borrower have previously entered into a Loan Agreement dated as of October 15, 2008 (as amended, the "Agreement").

B. Lender and Borrower wish to amend the Agreement as provided herein.

NOW, THEREFORE, in consideration of the premises and the mutual covenants and agreements herein contained, and for other good and valuable consideration, the receipt of which is hereby acknowledged, it is hereby agreed as follows:

1. The Agreement is amended as follows:

(i) The definitions of the following terms set forth in Schedule I to the Agreement are hereby amended to have the meanings set forth below:

"Financial Statements" means the audited financial statement of Borrower and each Guarantor for their fiscal years ended December 31, 2008 and the unaudited financial statement of Borrower and each Guarantor and for the quarter ended June 30, 2009.

"Maximum Principal Amount" means $18,400,000.00

"Scheduled Commitment Termination Date" means July 7, 2010.

(ii) ARTICLE VI: COVENANTS Section 6.02. Negative Covenants of the Agreement is hereby amended to add the following paragraph as a new subsection (f):

"(f) Borrower shall maintain a depository account with RBS Citizens Bank, N.A. as with a balance of at least Two-Hundred Fifty-Thousand Dollars and 00/100 ($250,000.00) until all Obligations of Borrower to Lender under the Agreement are indefeasibly paid in full."

(iii) ARTICLE VII: EVENT OF DEFAULT Section 7.01(K) is hereby amended to read in its entirety as follows:

"(k) At any time Borrower shall be a guarantor of obligations under such Loan Agreement, an of Event of Default shall exist under and as defined in that certain Loan Agreement dated September 30, 2009 between Lender and REGULUS THERAPEUTICS INC."

2. This Amendment may be executed in several counterparts, each of which shall be an original and all of which shall constitute but one and the same instrument.

3. All other terms and conditions of the Agreement not specifically amended by this Amendment shall remain in full force and effect and are hereby ratified and confirmed by Lender and Borrower.

4. This Amendment shall be governed by the law of the State of Illinois (without regard to the conflict-of-laws principles thereof).

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK;
EXECUTION PAGE FOLLOWS]

IN WITNESS WHEREOF, the parties hereto have executed this Amendment in their respective corporate names by their duly authorized officers, all as of the date first written above.

Lender: **RBS ASSET FINANCE, INC.**,
a New York corporation

By /s/ Cynthia Prince

Name Cynthia Prince

Title VP

Borrower: **ISIS PHARMACEUTICALS, INC.**,
a Delaware corporation

By /s/ B. Lynne Parshall

Name B. Lynne Parshall

Title COO & CFO

[EXECUTION PAGE OF AMENDMENT TO LOAN AGREEMENT]

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

AMENDMENT NO. 1 TO
AMENDED AND RESTATED LICENSE AGREEMENT

THIS AMENDMENT NO. 1 TO AMENDED AND RESTATED LICENSE AGREEMENT (the "Amendment") is made and entered into effective as of December 18, 2009 (the "Amendment No. 1 Effective Date"), by and between ONCOGENEX TECHNOLOGIES INC., having offices at #400 — 1001 West Broadway, Vancouver, B.C. V6H 4B1 ("OncoGenex"), and ISIS PHARMACEUTICALS, INC., having principal offices at 1896 Rutherford Road, Carlsbad CA 92008-7208 ("Isis"). OncoGenex and Isis each may be referred to herein individually as a "Party," or collectively as the "Parties."

WHEREAS, the Parties entered into an Amended and Restated License Agreement dated as of July 2, 2008 (the "Restated Agreement") under which Isis granted to OncoGenex the unilateral rights to continue the development and commercialization of OGX-011, a second generation antisense inhibitor of Clusterin;

AND WHEREAS, the Parties now wish to amend certain provisions of the Restated Agreement, as provided herein.

NOW, THEREFORE, the Parties do hereby agree as follows:

ARTICLE 1
DEFINITIONS

Capitalized terms used in this Amendment and not otherwise defined herein have the meanings ascribed to such terms as set forth in the Restated Agreement.

ARTICLE 2
AMENDMENT OF RESTATED AGREEMENT

2.1 Amendment re Section 5.3.2. Section 5.3.2 of the Restated Agreement is hereby amended to read in its entirety as follows:

"**5.3.2** To the extent that [***] OncoGenex under this Agreement collects safety and tolerability data or information specifically regarding a Product, OncoGenex will obtain from such sublicensee (a) the right to provide to Isis (whether through OncoGenex or its Affiliate, or directly from such sublicensee) the [***] described in [***], and (b) the right of Isis to [***] for the purposes described in [***]. Only sublicensees that actually provide such [***] and grant Isis the right to use such [***] as set forth herein, will have the right to access the results of any queries requested by OncoGenex. If and when Isis identifies safety, pharmacokinetic or other related issues that may be relevant to a Product [***] Isis will promptly inform OncoGenex of such issues, and if requested, provide the data and information supporting Isis' conclusions regarding such issues. In addition, at OncoGenex' or its sublicensee's (provided that such sublicensee provides the data, information and rights described above in this Section 5.3.2) reasonable request and at no cost to OncoGenex or its sublicensee, Isis will [***] the Isis Database to provide OncoGenex or its sublicensee information regarding [***] or other related issues."

2.2 Amendment re Section 6.5. Cell (a) of the first column in the table set forth in Section 6.5 of the Restated Agreement is hereby amended to read in its entirety as follows:

"(a) Prior to the initiation [***] of a first Registration Clinical Trial for a Product"

2.3 Addition of Section 6.11. A new Section 6.11 is hereby added to the Restated Agreement as follows:

"If after the Amendment No. 1 Effective Date, OncoGenex is the subject of a change of control with a Third Party, where the surviving company immediately following such change of control has the right to develop and sell the Product, then (i) a milestone payment of $20,000,000 will be due and payable to Isis 21 days following the first commercial sale of the Product in the United States; and (ii) the royalty rate payable under Section 6.2.1 will thereafter be [***] payable under such Section; *provided*, any Non-Royalty Revenue payments made to Isis under Section 6.5 prior to the payment of the $20,000,000 milestone under this Section 6.11 will be creditable against such milestone payment. If (a) OncoGenex grants a sublicense under this Agreement and the corresponding royalty rate is established under Section 6.2.1, and (b) such sub-licensee later acquires OncoGenex in a change of control, then notwithstanding subsection (ii) of this Section 6.11, the royalty rate payable under Section 6.2.1 in connection with such sublicense immediately prior to such change of control will apply to the surviving company after such change of control."

2.4 Amendment re Section 7.2.2(b). Section 7.2.2(b) of the Restated Agreement is hereby amended to read in its entirety as follows:

"**(b)** In addition, each Party will use reasonable efforts to notify (and provide as much advance notice as possible to) the other of any event materially related to Product (including any regulatory approval) of which the Party becomes aware so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event."

2.5 Addition of Section 7.2.2(c). A new Section 7.2.2(c) is hereby added to the Restated Agreement as follows:

"(b) Notwithstanding the foregoing, upon Isis' written request, OncoGenex or its sublicensees will include in press releases or oral public presentations that contain new material clinical data, regulatory approvals or other material information regarding a Product or this Agreement, a statement acknowledging the Parties' joint discovery and initial development of OGX-011, substantially in the form as OncoGenex has used immediately prior to the Amendment #1 Effective Date, the fact that intellectual property related to antisense technology embodied in such Product was licensed from Isis, and Isis' ticker symbol (e.g., Nasdaq: ISIS)."

2.6 Amendment re Section 8.3.1(a). The last sentence of Section 8.3.1(a) of the Restated Agreement is amended to state: "In any case, Isis may not settle, or otherwise consent to an adverse judgment in, any action or proceeding with respect to such infringement in a manner that diminishes the rights or interests of OncoGenex or OncoGenex's sublicensee,

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without the prior written consent of both OncoGenex and OncoGenex's sub-licensee, such consent not to be unreasonably withheld or delayed."

2.7 Amendment re Section 9.3.1. Section 9.3.1 of the Restated Agreement is hereby amended to read in its entirety as follows: "Upon expiration of the Term of this Agreement in accordance with Section 9.1 and payment of all amounts owed pursuant to this Agreement, the licenses granted by Isis to OncoGenex under this Agreement will automatically become perpetual, irrevocable, fully-paid non-exclusive licenses."

2.8 Amendment re Section 12.2.1. Section 12.2.1 of the Restated Agreement is hereby amended to read in its entirety as follows:

"12.2.1 Failure to Pay. If OncoGenex is in material breach of OncoGenex' obligation to make a payment to Isis under Article 6, then Isis may deliver written notice of such breach to OncoGenex, with a required copy of such notice to OncoGenex's sub-licensee. OncoGenex will have thirty (30) days following such notice to cure such breach (and provided further that OncoGenex's sub-licensee may cure such breach by making payment to Isis of any amounts owed by OncoGenex, and Isis agrees to accept all such payments made by OncoGenex's sub-licensee). If OncoGenex and its sub-licensee have received written notice of such a payment breach from Isis, and such breach is not cured within the 30 day period, Isis may declare an uncured material breach hereunder upon thirty (30) days advance written notice to OncoGenex and such notice will effectively terminate this Agreement upon expiration of such thirty (30) day period."

2.9 Amendment re Section 12.2.2. Section 12.2.2 of the Restated Agreement is hereby amended to read in its entirety as follows:

"12.2.2 Discontinued Development.

(a) If OncoGenex materially breaches its diligence obligations under Section 4.4, then Isis shall have the right to give OncoGenex written notice of such breach describing such material breach in reasonably specific detail, and Isis must provide at the same time a copy of such notice to OncoGenex's sub-licensee. OncoGenex, or its sub-licensee, shall have the right to cure such breach within ninety (90) days after receipt of written notice from Isis (or longer if such breach is not reasonably curable with such 90 days), and Isis agrees to accept any performance by such sub-licensee in seeking to cure the breach. In the event of a Discontinuance or if OncoGenex materially breaches its diligence obligations under Section 4.4 and such material breach is not cured by OncoGenex and/or its sub-licensee within ninety (90) days after receipt of written notice from Isis (as provided above), then in any such case, as Isis' sole and exclusive remedy therefor, Isis will have the right to terminate the [***]under [***] upon thirty (30) days prior written notice to OncoGenex; *provided that*, if such breach is not reasonably curable within such 90 days, then as long as OncoGenex and/or its sub-licensee continues to take substantial steps toward curing such material breach until such breach is cured, Isis may not exercise its termination rights under this Section 12.2.2.

(b) Upon any such termination under subclause (a) above, OncoGenex will [***] Isis a [***], as the case may be, to the OncoGenex Product-Specific Technology, OncoGenex Patents, OncoGenex Technology and any Product-Specific Technology Patents assigned to OncoGenex under Section 4.2.1 (in the case of OncoGenex Patents and OncoGenex Technology that are the subject of one or more Third Party agreements, such license or sublicense shall be subject to all restrictions and obligations (including financial obligations) under such Third Party agreements) existing as of such date solely to develop, make, have made, use, sell, offer for sale, have sold and import Nonexclusive Clusterin ASOs (and any products containing such Nonexclusive Clusterin ASOs). For purposes of this Section 12.2.2, "Nonexclusive Clusterin ASOs" means ASOs that act predominantly by [***] Clusterin [***] or that are [***] to Clusterin [***], *provided, however* that the term "Nonexclusive Clusterin ASOs" expressly excludes: (a) OGX-011 and any other ASO that has the [***]; and (b) any other ASO that (i) acts to modulate [***] Clusterin and (ii) for which, at the time of such Discontinuance or uncured material breach, OncoGenex, its Affiliates or sublicensees have [***]. Within ninety (90) days following the effectiveness of any termination by Isis, pursuant to this Section 12.2.2, of the [***], OncoGenex shall provide Isis with a [***].

(c) OncoGenex covenants and agrees that any [***] granted by OncoGenex under the OncoGenex Product-Specific Technology, OncoGenex Patents, OncoGenex Technology and any Product-Specific Technology Patents assigned to OncoGenex under Section 4.2.1 will be expressly subject to the [***] that OncoGenex [***] Isis under subclause (b) above (if applicable) under such Patents under this Section 12.2.2, and such [***] by OncoGenex will automatically be limited by such [***] to Isis, [***] as above."

2.10 Addition of Section 12.2.3. A new Section 12.2.3 is hereby added to the Restated Agreement as follows:

"**12.2.3** Notwithstanding the foregoing, if Isis terminates the [***], and prior to such termination OncoGenex [***], then, provided [***], Isis shall [***]."

2.11 Amendment re Section 13.15. Section 13.15 of the Restated Agreement is hereby amended to add a new Section 13.15.7 that reads in its entirety as follows:

"**13.15.7** All notices that may or are given by Isis under this Section 13.15 to OncoGenex shall [***]"

2.12 Amendment re Appendix A. The definition of "Discontinuance" in Appendix A of the Restated Agreement is hereby amended to read in its entirety as follows:

"**'Discontinuance'** means OncoGenex voluntarily elects to abandon [***] all development and commercialization of Products, as evidenced by a written communication from an authorized officer of OncoGenex to Isis."

2.13 Amendment re Appendix A. The definition of "Revenue" in Appendix A of the Restated Agreement is hereby amended to read in its entirety as follows:

"**"Revenue"** means all revenues, receipts, monies, and the fair market value of all other consideration directly or indirectly collected or received whether by way of cash or credit or any barter, benefit, advantage, or concession received OncoGenex relating to the sale, license or any other commercial transaction involving OGX-011 and/or the Product, with the exception of the following: (i) any consideration received for the reimbursement for research and development activities and (ii) any consideration received for the fair market portion of any sale of equity or quasi-equity securities including, without limitation, common shares and preferred shares."

2.14 Based on the fact that OncoGenex has an obligation to disclose to Isis, under the Restated Agreement, certain confidential information that OncoGenex may receive from its sublicensees under the Restated Agreement, Isis agrees that, promptly after OncoGenex enters into such a sublicense agreement, Isis, OncoGenex and such sublicensee will enter into a mutual confidentiality agreement under which Isis will agree to protect the confidentiality of any such information disclosed by OncoGenex or OncoGenex's sublicensee to Isis pursuant to the Restated Agreement or the sublicense agreement on terms that are consistent with the confidentiality provisions of the Restated Agreement.

ARTICLE 3
REPRESENTATIONS AND COVENANTS RELATING TO AMENDMENT OF RESTATED AGREEMENT

3.1 Representations and Covenants Regarding Improvements and Technology. Isis hereby represents and warrants to OncoGenex that: (a) Isis has assigned to OncoGenex all rights, title, and interests in and to the Product-Specific Technology and the Product-Specific Technology Patents existing as of the Amendment No.1 Effective Date; and (b) to Isis' knowledge, Isis has transferred to OncoGenex all Information and technology required to be transferred under the first sentence of Section 4.2.2 of the Restated Agreement. Isis shall use reasonable efforts to determine whether any Information and technology required to be transferred under the first sentence of Section 4.2.2 has not been transferred to OncoGenex and, if so, shall promptly transfer such Information and technology to OncoGenex (such transfer to be at Isis' expense if the [***] set forth in Section 4.2.2 has not yet been reached, and otherwise at OncoGenex' expense).

3.2 Representations and Covenants Regarding Agreements. Isis hereby represents and warrants to OncoGenex that: (a) as of the Amendment No.1 Effective Date, Isis

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does not believe that OncoGenex is in breach of any of its obligations under the Restated Agreement; (b) the Restated Agreement is in good standing and in full force and effect; and (c) Isis' agreements with [***] are all in good standing and in full force and effect. Isis shall use good faith efforts not to breach any of the terms of any such agreements.

ARTICLE 4
MISCELLANEOUS

4.1 Integration. This Amendment is deemed integrated into and made part of the Restated Agreement, and is governed by all applicable terms of the Restated Agreement. This Amendment modifies the applicable terms of the Restated Agreement solely as provided above. All other terms, obligations, and conditions of the Restated Agreement are and shall remain in full force and effect. To the extent this Amendment is in conflict with any terms of the Restated Agreement, this Amendment shall control.

4.2 This Amendment automatically terminates upon termination of the Restated Agreement.

4.3 This Amendment may be executed in one or more counterparts by the parties by signature of a person having authority to bind the party, which may be by facsimile signature, each of which when executed and delivered, by facsimile transmission or by mail delivery, will be an original and all of which will constitute but one and the same Amendment.

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IN WITNESS WHEREOF, the Parties hereto have caused this Amendment to be executed by their duly authorized representatives as of the date first above written.

ONCOGENEX TECHNOLOGIES INC.	**ISIS PHARMACEUTICALS, INC.**
Per: /s/ Scott D. Cormack	Per: /s/ B. Lynne Parshall
Scott D. Cormack, President & CEO	B. Lynne Parshall COO and CFO

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Isis Pharmaceuticals Singapore Pte Ltd., a Singapore Limited Private Company

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Regulus Therapeutics Inc., a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269) of Isis Pharmaceuticals, Inc. and the related Prospectus of our reports dated March 1, 2010, with respect to the consolidated financial statements Isis Pharmaceuticals, Inc., and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in the Annual Report (Form 10-K) for the year ended December 31, 2009.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2010

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: March 1, 2010

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, B. Lynne Parshall, 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: March 1, 2010

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
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 B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2009, 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: March 1, 2010

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
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.