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, 2010

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 x No o

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

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Select Market was $779,460,375 as of June 30, 2010.*

The number of shares of voting common stock outstanding as of February 22, 2011 was 99,578,748.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 28, 2011 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 16, 2011 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 70 to 74 incorporates several documents by reference as indicated therein.

* Excludes 17,665,397 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, 2010. 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 jointly 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 thera peutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

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

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

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 we include on or link to our Internet site is not a part of this report or any registration statement that incorporates this report by reference. You may also read and copy our filings at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information sta tements, 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 clinical value inflection points. In this way, our organization remains small and focused. We discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of qua lity partners with late-stage development and commercialization expertise. For example, we partner with leading pharmaceutical companies that have late-stage development, commercialization and marketing expertise, such as Bristol-Myers Squibb, Genzyme Corporation, GlaxoSmithKline, or GSK, and Eli Lilly and Company. We also work with a consortium of smaller companies that can exploit our technology outside our primary areas of focus using 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 through collaborations with Alnylam

Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities such as through collaborations with Achaogen, Inc., or Achaogen, and Archemix Corp., or Archemix, Beyond human therapeutics, we benefit from the commercialization of products incorporating our technology by other companies that are better positioned to maximize the commercial potential of these inventions, such as when we sold our subsidiary Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, a wholly owned subsidiary of Abbott Laboratories. All of these different types of relationships are part of our unique business model and create current and future shareholder value.

Through the power and efficiency of our technology, we can add new antisense drugs to our development pipeline each year. Over the past two years, we have added six new drugs to our pipeline, including drugs in each of our core therapeutic areas. These drugs offer new approaches to treat disease and broaden our therapeutic focus. For example, the new drugs we added to our cardiovascular franchise expand our cardiovascular approach beyond managing cholesterol and other atherogenic lipids to reducing inflammatory and thrombotic factors, which can contribute significantly to cardiovascular disease. Because we can discover more drugs than we can develop ourselves, our partnership strategy allows us to focus on our key therapeutic areas while also creating an expansive pipeline with multiple partnerships. We focus our research and development efforts primarily in cardiovascular, metabolic, severe and rare, 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. We and Genzyme reported positive data from four Phase 3 studies demonstrating consistent and robust lowering of low-density lipoprotein cholesterol, or LDL-C, and other atherogenic lipids. Across these four studies, treatment with mipomersen reduced LDL-C in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. Mipomersen also reduced many other atherogenic lipids, including triglycerides,

lipoprotein a, or Lp(a), and non-high-density lipoprotein cholesterol, or non HDL-C, due to its unique mechanism of action. We believe the safety profile of mipomersen supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. The m ipomersen data from all four of our Phase 3 studies support the profile of the drug as a novel treatment to reduce LDL-C in patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

Our clinical experience with mipomersen demonstrates that antisense drugs work in man. 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. Over the past couple of years, we and our partners have reported positive data from five Phase 2 studies and seven Phase 1 studies. For example, we reported data from a positive Phase 2 study 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 characteristics create an encouraging profile for a new therapy to treat type 2 diabetics. Many of our partnered drugs are also showing encouraging activity in numerous diseases. Our partner, Excaliard Pharmaceuticals, Inc., or Excaliard, reported data from three Phase 2 studies showing tha t treatment with EXC 001, a locally administered antisense drug, significantly reduced scarring in patients. 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 $830 million in payments from licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our current partnered programs we have the potential to earn more than $3.5 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 that incorporate our inventions that other companies are developing and commercializing. For example, together with Alnylam, we created and jointly own Regulus. Regulus takes advantage of the technology, expertise and intellectual property of its founding companies to lead the field of microRNA therapeutics. We have the opportunity to share in Regulus' successes as Regulus advances its partnered drug programs forward and to benefit from the appreciation in the value of our investment in Regulus.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. As an innovator in RNA-based drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, 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 2010 and early 2011.

2010 and Early 2011 Business Highlights

Drug Development Highlights

- Mipomersen continues to advance in clinical development and move closer to the market for patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. We and Genzyme successfully completed four Phase 3 studies that the companies plan to include in the initial United States and European filings for marketing approval for mipomersen. These filings will seek approval for the treatment of patients with homozygous familial hypercholesterolemia, or hoFH, in the United States and Europe. The European filing may also include patients with severe heterozygous familial hypercholesterolemia, or severe heFH. Genzyme is also preparing for filings in markets beyond the United States and Europe.
  - The table below briefly summarizes the results of these trials. In all four studies, all primary, secondary and tertiary endpoints were met.

Phase 3 Study	Average Baseline LDL-C (mg/dL)	Average LDL-C Reduction (mg/dL)	Placebo Change in LDL-C (%)	Mipomersen Change in LDL-C (%)
Homozygous FH	426	-106	-3.3	-24.7
Severe Hypercholesterolemia	276	-101	+13	-36
Heterozygous FH	153	-46	+5	-28
High-Risk	123	-48	-5	-37

  - In all studies, frequently observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases, as seen in previous studies.
  - In all studies, patients maintained a regimen of maximally tolerated lipid-lowering therapy.
- We and our partners continued to advance the drugs in our pipeline and reported clinical results in a broad range of diseases, including positive clinical Phase 1 data on six drugs. We added three new drugs to our pipeline.
- We and our partners initiated Phase 1 clinical studies on four drugs, initiated seven Phase 2 studies on four drugs, and initiated two Phase 3 studies on OGX-011.

Corporate Highlights

- We formed a new strategic alliance worth up to nearly $1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases. We received a $35 million upfront payment and a $5 million milestone payment related to the identification of ISIS-GSK1$_{Rx}$, the first drug selected as part of our collaboration with GSK.
- We and Bristol-Myers Squibb extended our collaboration by two years to discover a more potent PCSK9 drug to move forward in development.
- Regulus formed a new alliance with sanofi-aventis worth potentially over $750 million to develop and commercialize microRNA therapeutics, including Regulus' leading fibrosis program targeting miR-21. We received $1.9 million, which represents 7.5 percent of the $25 million upfront payment Regulus received from sanofi-aventis.
- sanofi-aventis invested $10 million in Regulus, valuing Regulus at more than $130 million. From this investment sanofi-aventis acquired less than 10 percent ownership of Regulus, leaving us with 46 percent ownership.

- Regulus and GSK established a new collaboration to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for hepatitis C viral infection.
- We earned in excess of $15 million in milestone payments and sublicensing fees in 2010 as our partners advanced drugs in development.

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Development Projects

We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets we can build a large and diverse portfolio of drugs designed to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, ocular, severe and rare, 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 impac t 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. In 2010, we selected our generation 2.5 chemistry, an advancement that we believe will increase the potency of our drugs and make oral administration commercially feasible. We expect that these generation 2.5 drugs will constitute some of our future drugs and may serve as follow-on drugs to some of our current drugs in development.

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 when compared to small molecules.

We and our partners are developing antisense drugs for systemic, intrathecal and local 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 EXC 001 or iCo-007. 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 obt ained 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.

Cardiovascular disease is an area of focus for us. We believe that antisense drugs could have a significant impact in patients with high cardiovascular risk. These are patients who are on a regimen of cardiovascular disease therapies and who are still at high risk for a cardiac event or death. The liver is an ideal target organ for cardiovascular disease therapies, and antisense drugs in particular, because there are many liver-produced targets that affect the production of cholesterol particles, clotting factors and other factors that contribute to the inflammatory components of cardiovascular disease. Our antisense drugs distribute to the liver and inhibit the production of many targets associated with cardiovascular risk, creating an opportunity for us to develop many complementary and effective antisense drugs for cardiovascular disease.

Mipomersen — Mipomersen is a novel first-in-class apo-B synthesis inhibitor in development. Mipomersen is a second-generation antisense drug we discovered and licensed to Genzyme in 2008. Mipomersen acts by decreasing the production of apolipoprotein-B, or apo-B. Apo-B provides the structural core for all atherogenic lipids, including LDL-C, which carry cholesterol through the bloodstream. Mipomersen reduces LDL-C and other atherogenic lipids linked to cardiovascular disease by preventing their formation.

Mipomersen is being developed to treat patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. These patients can be diagnosed as having familial hypercholesterolemia, or FH. FH is a genetic disease in which patients cannot properly metabolize LDL-C, resulting in elevated LDL-C levels. HoFH is a rare form of FH. HoFH patients can have LDL-C levels greater than 600 mg/dL and are at very high risk for early coronary events and sudden death. Severe heFH patients comprise a small subset of heterozygous FH patients, a more common form of the disorder. Severe heFH patients have LDL-C levels greater than 200 mg/dL with coronary artery disease or more than 300 mg/dL without coronary artery disease despite maintaining a regimen of maximally tolerated lipid-loweri ng therapy. Patients with untreated FH have a 50 percent mortality rate by age 60.

Together with Genzyme, we have evaluated mipomersen in four positive Phase 3 studies in which all primary, secondary and tertiary endpoints were met. In all four Phase 3 studies, treatment with mipomersen lowered LDL-C and reduced other atherogenic lipids, including apo-B, Lp(a), triglycerides and very-low density lipoprotein, or VLDL. Many of these lipids are generally accepted risk factors for cardiovascular disease. In all studies, frequently observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases, as seen in previous studies.

Genzyme will initially seek marketing approval for mipomersen for the treatment of patients with hoFH in the United States and Europe. The European filing may also include patients with severe heFH. Due to the size of the severe heFH population, the FDA provided guidance for additional 12

month exposure data before the mipomersen filing for severe heFH in the United States. The Genzyme team will work with the FDA to further define the study required. The FDA acknowledged that an outcome study may not be feasible in severe heFH patients due to the size of the population. Genzyme is also preparing for filings in markets beyond the United States and Europe. Two of our Phase 3 studies evaluated mipomersen in patients with hoFH and severe hypercholesterolemia who were on substantial lipid lowering therapy. In both of these studies, the average reduction of LDL-C w as greater than 100 mg/dL.

Phase 3 Study	Average Baseline LDL-C (mg/dL)	Average LDL-C Reduction (mg/dL)	Placebo % Change in LDL-C	Mipomersen % Change in LDL-C	
Homozygous FH	426	-106	-3.3	-24.7	100 mg/dL average reduction in LDL-C
Severe Hypercholesterolemia	276	-101	+13	-36	100 mg/dL average reduction in LDL-C

Together with Genzyme, we also evaluated mipomersen in two additional phase 3 studies in patients with heterozygous FH and in patients with high cholesterol at high risk for coronary heart disease who were on substantial lipid lowering therapy. As with the two previous studies, all primary, secondary and tertiary endpoints were met, including reduction in apo-B, Lp(a), triglycerides, total cholesterol, non HDL-C and VLDL.

Phase 3 Study	Average Baseline LDL-C (mg/dL)	Average LDL-C Reduction (mg/dL)	Placebo % Change in LDL-C	Mipomersen % Change in LDL-C	
Heterozygous FH	153	-46	+5	-28	45% of Patients Achieved less than 100 mg/dL
High-Risk	123	-48	-5	-37	51 % of Patients Achieved less than 70 mg/dL

In addition to observing LDL-C lowering, we believe the emerging safety profile of mipomersen will support our initial plan for mipomersen to be used in patients who, despite being treated with maximally tolerated lipid-lowering therapies, are far from their recommended LDL-C goal. These are patients who are in the greatest need and who have had one or more major cardiovascular events.

Genzyme is developing a comprehensive plan to address this new commercial market that consists of patients who are in desperate need of new treatment options. A key to Genzyme's strategy is to increase awareness of FH, an under-diagnosed, condition. Genzyme plans to concentrate marketing and sales efforts on lipid specialists and physicians who refer patients to these specialists, using its expertise in identifying unique and underserved patients. We believe Genzyme has the commercial infrastructure and aptitude to successfully commercialize mipomersen worldwide making the drug available for patients in need.

In summary, the performance of mipomersen has been consistent across the entire Phase 3 program, supporting our initial market focus in patients, who despite being treated with maximally tolerated lipid-lowering therapies, are far from their recommended LDL-C goal and as a result are at high risk of a cardiovascular event or death. Genzyme plans to file for marketing approval of mipomersen in both the United States and Europe in 2011.

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.&# 160; This evidence suggests that we might help patients who are at risk for coronary events by significantly decreasing their CRP levels. In addition, clinicians have associated elevated CRP levels with a worsening of overall outcomes in conditions such as end-stage renal disease and multiple myeloma, suggesting that lowering CRP could help these patients. CRP elevation is also evident in many other major inflammatory diseases such as Crohn's disease and rheumatoid arthritis.

In preclinical studies,we observed that our antisense inhibitor of CRP suppressed liver and serum CRP levels. We evaluated ISIS-CRP$_{Rx}$ in a Phase 1 blinded, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of our drug. In this study, ISIS-CRP$_{Rx}$ produced statistically significant reductions in CRP in the cohort of subjects that entered the study with elevated levels of CRP. In all subjects evaluated, ISIS-CRP$_{Rx}$ was well tolerated. Our Phase 2 plan for ISIS-CRP$_{Rx}$ is to evaluate the drug in diseases with elevated CRP that could provide early proof-of-concept. Initially we plan to evaluate ISIS-CRP$_{Rx}$ in patients with multiple myeloma and rheumatoid arthritis before expanding into cardiovascular and other diseases. The data from these initial Phase 2 studies will inform the development path for ISIS-CRP$_{Rx}$, in which we could expand into other diseases.

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. PCSK9's 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 PCS K9 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, we established a collaboration with Bristol-Myers Squibb to identify antisense drugs that target PCSK9. In 2008, Bristol-Myers Squibb selected a drug to advance into clinical development. In 2010, Bristol-Myers Squibb stopped the Phase 1 study of BMS-PCSK9$_{Rx}$, and discontinued development of the drug and plans to discover a more potent PCSK9 antisense drug under its extended collaboration with us.

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 that is an important component of the coagulation pathway. Because of its role in the intrinsic coagulation pathway, inhibition of Factor XI could offer an effective approach for preventing the formation of blood clots with a lower risk of bleedi ng. High levels of Factor XI are a risk factor for aberrant blood clot

formation, which is the leading cause of morbidity and mortality associated with vascular diseases, including heart attack, deep vein thrombosis and stroke. Blood clot formation is also a common complication of surgical procedures, especially orthopedic surgeries such as knee or hip replacement. Most commonly used therapeutics reduce clotting but also produce an unacceptable increase in bleeding risk. In preclinical studies, ISIS-FXI$_{Rx}$ demonstrated potent antithrombotic activity with no increase in bleeding compared with standard anti-clotting agents, including low molecular weight heparin, warfarin and Factor Xa inhibitors, all of which increased bleeding. Furthermore, humans who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleed ing risk. We are currently evaluating ISIS-FXI$_{Rx}$ in a Phase 1 study in healthy volunteers.

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. Genetic studies in humans have associated lower levels of apoC-III with lower triglycerides levels. In addition, lower levels of apoC-III appeared to improve health and extend longevity. In preclinical studies, ISIS-APOCIII$_{Rx}$ mitigated symptoms of metabolic syndrome and reduced atherosclerosis in mice. We are currently evaluating ISIS-APOCIII$_{Rx}$ in a Phase 1 study.

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. Our research efforts include targeting lipoprotein (a), Lp(a), an atherogenic particle and a recognized independent cardiovascular risk factor. Unlike LDL-C or apoB, Lp(a) is not modified by most lipid-lowering therapies currently available, including statins. We believe that targeting Lp(a) could provide an alternate approach to lipid management complementary to lipid lowering therapies, including mipomersen.

Metabolic Franchise

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

Metabolic disease is a very large area of medical need and is another area where we focus our drug discovery efforts. We are developing antisense drugs that doctors could add to existing therapies to treat diabetes and obesity. One hurdle for traditional drug development is the selective targeting of a disease-causing protein from closely related proteins. We design our antisense drugs to target the gene that is responsible for producing the disease-causing protein while avoiding unwanted activity associated with inhibiting a closely related protein. This design makes antisense drugs significantly more selective than many other therapeutic approaches. In addition, the liver and fat cells produce many of the most important therapeutic targets for metabolic disease. Our antisense drugs distribute to the liver and fat cells and inhibit the production of these ke y therapeutic targets. Our newest drug to enter development, ISIS-FGFR4$_{Rx}$, is an anti-obesity drug that inhibits the production of FGFR4 in fat cells and offers a new mechanism for weight control that may be complementary to appetite-suppressing therapies currently on the market.

ISIS-PTP1B$_{Rx}$ — Our most advanced program in metabolic disease targets protein tyrosine phosphatase-1B, PTP-1B, a phosphatase that negatively regulates insulin receptor signaling. PTP-1B is responsible for turning off the activated insulin receptor, so reducing PTP-1B enhances insulin activity. Scientists have long recognized PTP-1B as an attractive target to treat diabetes, but due to structural similarities among closely related proteins, pharmaceutical companies have had difficulty identifying small molecule drugs with sufficient specificity to be safe. Our a ntisense technology allows us to design specific drugs that inhibit PTP-1B without inhibiting other protein family members. This mechanism makes it possible to reduce PTP-1B activity without affecting other closely related proteins that, when inhibited, could lead to unwanted side effects.

Our most advanced antisense drug in our PTP-1B program is ISIS 113715. In two Phase 2 studies, treatment with ISIS 113715 improved glucose control in patients with type 2 diabetes.

- In the first Phase 2 study, we evaluated ISIS 113715 as a single agent in newly diagnosed type 2 diabetic patients. Treatment with ISIS 113715 resulted in a statistically significant improvement in multiple measures of glucose control.
- In the second Phase 2 study, we evaluated ISIS 113715 in patients with type 2 diabetes who had uncontrolled blood sugar despite treatment with stable doses of sulfonylurea. Treatment with ISIS 113715 resulted in 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-C. Furthermore, consistent with the preclinical data with ISIS 113715, we observed a tendency toward weight loss 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.

In both studies, ISIS 113715 demonstrated a favorable safety profile with no exacerbation of sulfonylurea-induced hypoglycemia or other clinically significant adverse effects.

Our preclinical and clinical data demonstrate the broad therapeutic potential of inhibiting PTP-1B. In addition to glucose control, this profile includes the reduction of LDL-C, a potentially significant benefit for patients with type 2 diabetes who are at high cardiovascular risk, and the potential to reduce weight. We are currently completing long-term toxicology studies for our PTP-1B program, including evaluating a significantly more potent drug. Based on the significant potency difference we observed between the newer antisense drug and ISIS 113715, instead of developing ISIS 113715 we plan to begin clinical development on the more potent PTP-1B inhibitor in 2011.

ISIS-GCGR$_{Rx}$ — ISIS-GCGR$_{Rx}$ is an antisense drug that targets GCGR, or glucagon receptor. 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 reported Phase 1 data in which our most advanced GCGR drug 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 this drug showed a dose-dependent decrease in blood glucose levels and at a dose of 400 mg/week demonstrated statistically significant decreases in blood glucose following the glucagon infusion ($p<0.0001$).

In parallel with completing a Phase 1 study for our GCGR drug, we identified a more potent antisense inhibitor to GCGR. A more potent drug should enhance the therapeutic profile of the GCGR program and provide much greater commercial value. We plan to begin clinical development on this more potent drug in 2011.

ISIS-GCCR$_{Rx}$ — ISIS-GCCR$_{Rx}$ is an antisense drug that targets GCCR, or glucocorticoid receptor. 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 delivered systemically 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 plan to move a GCCR drug into clinical development in 2011.

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 negatively affecting 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 generally healthy. Therefore, we believe that ISI S-SGLT2$_{Rx}$ could be a potent, highly active drug that will provide significant therapeutic benefits.

We are currently 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 initiate a Phase 2 study in 2011.

ISIS-FGFR4$_{Rx}$ — ISIS-FGFR4$_{Rx}$ is an antisense drug that targets fibroblast growth factor receptor 4, or FGFR4, in the liver and fat tissue. FGFR4 helps regulate energy expenditure and body weight. We designed ISIS-FGFR4$_{Rx}$ to treat obesity by increasing metabolism, particularly by increasing lipid and fat burn ing. ISIS-FGFR4$_{Rx}$ should not reduce FGFR4 expression in the CNS or heart, thereby avoiding the CNS and cardiovascular side effects associated with many obesity drugs in development.

In preclinical studies, antisense inhibition of FGFR4 lowered body weight when administered as a single agent and in the presence or absence of a calorie-restricted diet. Additionally, inhibition of FGFR4 produced a decrease in body weight when administered in combination with an appetite-suppressing drug. In addition to the reduction in body weight, inhibiting FGFR 4 demonstrated an improvement in insulin sensitivity. ISIS-FGFR4$_{Rx}$ was safe and well tolerated in multiple species. ISIS-FGFR4$_{Rx}$ utilizes technology we in-licensed from Verva Pharmaceuticals. ISIS-FGFR4$_{Rx}$ is the first drug in our metabolic franchise to treat obesity. We plan to begin investigational new drug enabling, or IND-enabling, studies on ISIS-FGFR4$_{Rx}$ in the first half of 2011.

Cancer Franchise

We are pursuing the discovery and development of antisense drugs to treat cancers both internally and through our partnerships with Eli Lilly and Company and OncoGenex Technologies Inc. Cancer is an area of significant unmet medical need and an area where our antisense technology provides us with unique advantages in discovering new drugs. Cancer is an extremely complex disease that involves a large number of targets. Our technology allows us to evaluate a very broad and diverse range of targets and identify their involvement in different types of cancers. The information we gain early in development on each of these targets allows us to make informed development decisions and quickly determine the targets that would be most effective for an anti-cancer drug. In addition, we select anti-cancer targets that provide a multi-faceted approach to treating can cer. We develop drugs to targets that are directly involved in cancer growth, migration or survival, such as our STAT3 drug. We also evaluate drugs to targets that are indirectly linked to cancer growth, such as inflammatory processes. For example, in patients with multiple myeloma, elevated levels of the inflammatory marker, CRP, are predictive of worse outcomes. We have an inhibitor to CRP that we plan to evaluate in multiple myeloma and other diseases.

Our cancer pipeline consists of anti-cancer antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. In late 2010, we initiated a Phase 2 program for our anti-cancer drug, ISIS-EIF4E$_{Rx}$ in patients with non-small cell lung cancer, or NSCLC, and prostate cancer. Because eIF-4E, or eukaryotic initiation factor-4E, is a target that is involved in many cellular processes critical to tumor cell growth and survival, we believe that inhibiting eIF-4E could provide therapeutic benefit in numerous cancers. In addition to ISIS-EIF4E$_{Rx}$ our current portfolio consists of four an tisense drugs. Over the past couple of years, our partners presented encouraging clinical data on a number of antisense drugs, including positive Phase 2 overall median survival data for OGX-011 and positive Phase 1 data on LY2181308 and OGX-427. 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 the anti-cancer drugs in our pipeline demonstrate how uniquely suited our technology is to create novel cancer therapeutics. Because of these observations, cancer is one of our core therapeutic areas and an area in which we continue to expand our efforts 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. Teva is studying OGX-011 for use as an adjunct therapy to enhance the effectiveness of chemotherapy. OGX-011 has shown promising results in combination with currently available chemotherapies in several tumor types. The FDA 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-0 11 to Teva as part of a global license and collaboration agreement to develop and commercialize OGX-011.

OncoGenex evaluated OGX-011 in five Phase 2 studies in combination with various cancer therapies for prostate, NSCLC and breast cancer. OncoGenex reported results from a randomized Phase 2 study of OGX-011 in patients with advanced metastatic castrate resistant prostate cancer, or CRPC. In this study, OncoGenex reported a median overall survival of 23.8 months in patients treated with 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 treatment with OGX-011 was well tolerated in combination with docetaxel.

OncoGenex has also evaluated OGX-011 in a Phase 1/2 combination study in patients with 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 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. In 2010, OncoGenex and Teva initiated two Phase 3 clinical studies of OGX-011 in patients with prostate cancer. 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 as first-line treatment in patients with advanced, inoperable NSCLC in 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 may 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 survi vin messenger RNA, or mRNA, and protein levels in tumor cells.

Eli Lilly and Company is evaluating LY2181308 as a combination therapy in two separate randomized Phase 2 studies: one, in patients with advanced/metastatic NSCLC who failed first line chemotherapy treatment; second, in patients with hormone refractory prostate cancer who receive docetaxel for first line chemotherapy. In addition, Eli Lilly and Company has completed a proof-of-concept Phase 2a study in patients with refractory acute myeloid leukemia.

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

Eli Lilly and Company completed a Phase 1 study of ISIS-EIF4E$_{Rx}$ in patients with cancer that showed that the drug was well tolerated at doses up to 1200 mg per week. Eli Lilly and Company has rights to license ISIS-EIF4E$_{Rx}$ from us on predefined terms. In 2010, we initiated a Phase 2 program of ISIS-EIF4E$_{Rx}$ in patients with NSCLC and prostate cancer.

OGX-427 — 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 June 2010, 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 as well as in combination with docetaxel. In addition, OGX-427, when used as a single agent, demonstrated declines in circulating tumor cells at all doses and in all diseases 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.

OncoGenex is evaluating OGX-427 in a Phase 1 study in patients with bladder cancer and a Phase 2 study in men with metastatic prostate cancer. OncoGenex announced that it plans to initiate a Phase 2 study evaluating OGX-427 as a first-line treatment for metastatic bladder cancer in 2011.

ISIS-STAT3$_{Rx}$ — We designed ISIS-STAT3$_{Rx}$ to treat cancer by inhibiting the production of a gene critical for tumor cell growth and survival. Signal transducer and activator of transcription 3, or STAT3, is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma and promotes tumor cell growth and prevents cell death. In preclinical studies, ISIS-STAT3$_{Rx}$ demonstrated antitumor activity in animal models of human cancer with an attractive safety profile. We will evaluate ISIS-STAT3$_{Rx}$ in a variety of cancers where scientists believe STAT3 plays a key role, such as liver cancers and multiple myeloma. We plan to initiate IND-enabling studies on ISIS-STAT3$_{Rx}$ in 2011.

Severe & Rare / Neurodegenerative Franchise

We are pursuing the discovery and development of antisense drugs for severe and rare diseases in which there is a need for new treatment options. According to the National Institutes of Health, or NIH, there are approximately 5,000 to 8,000 rare diseases, many life-threatening or fatal. Unfortunately there are few effective therapeutics available to treat many of these severe and rare diseases. Most of these diseases are genetic or have a genetic component. In some cases, the onset of disease is characterized by the presence of a protein that, through a genetic defect, cannot function properly in the cell. In order to treat these diseases, we can discover and develop antisense drugs that selectively inhibit the production of only the disease-causing protein. In other cases, alternative splicing can result in the omission of proteins that are critical for norm al cellular function. Using antisense technology, we can direct alternate splicing to potentially correct for a genetic defect. For example, our drug, ISIS-SMN$_{Rx}$, increases the production of a protein that is necessary for normal motor function but that is absent in disease.

Many neurodegenerative diseases are characterized as severe and rare diseases. Our most advanced neurodegenerative drug is ISIS-SOD1$_{Rx}$, an antisense drug to treat amyotrophic lateral sclerosis, or ALS, also known as Lou Gehrig's disease.

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 th is 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 are evaluating ISIS-SOD1$_{Rx}$ in a Phase 1 study in patients with the familial form of ALS.

ISIS-SMN$_{Rx}$ — ISIS-SMN$_{Rx}$ is an antisense drug designed to treat spinal muscular atrophy, or 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 NIH's National Institute of Neurological Disorders and Stroke. A genetic deleti on of the survival motor neuron 1, or SMN1, gene is responsible for SMA. ISIS-SMN$_{Rx}$ increases the production of the SMN protein 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.

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$_{Rx}$. ISIS-SMN$_{Rx}$ utilizes technology we in-licensed from the University of Massachusetts. We plan to begin clinical development with ISIS-SMN$_{Rx}$ in 2011.

ISIS-GSK1$_{Rx}$ — ISIS-GSK1$_{Rx}$ is an antisense drug designed to treat an undisclosed serious and rare disease. ISIS-GSK1$_{Rx}$ is the first drug to enter development under our partnership with GSK. We receive milestone payments from GSK as ISIS-GSK1$_{Rx}$ advances in development, and we are responsible f or development of the drug up to Phase 2 proof-of-concept, at which time GSK has the option to license ISIS-GSK1$_{Rx}$ from us. We plan to begin clinical development with ISIS-GSK1$_{Rx}$ in 2011.

Other Drugs in Development

The broad applicability of our antisense technology allows us to create promising drugs in a variety of disease areas. We have successfully developed novel drugs and licensed 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. For instance, our partner, Excaliard, presented data from three Phase 2 studies demonstrating that EXC 001 reduced scarring in patients.

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. Achaogen reported the successful compl etion of a Phase 1 study on ACHN-490 and initiated a Phase 2 study on ACHN-490.

Alicaforsen — Now under license to Atlantic Pharmaceuticals Limited, alicaforsen is an antisense drug that targets intercellular adhesion molecule 1, or ICAM-1. ICAM-1 is over-expressed in a wide variety of inflammatory disorders, including ulcerative colitis and pouchitis. Ulcerative colitis, or UC, is an inflammatory bowel disease, or IBD, of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in UC patients who have had their diseased colons removed. In 2007, we licensed alicaforsen to Atlantic Pharmaceuticals for pouchitis, UC and other inflammatory diseases. The FDA and European Medicines Agency, or EMEA, have since granted alicaforsen Orphan Drug Designation for the treatment of pouchitis in the United States and Europe respectively. Atlantic Pharmaceuticals currently supplies alicaforsen in response to physicians' requests under international Named Patient Supply regulations for patients with IBD. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

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

ATL1103 — ATL1103 is an antisense drug that targets the growth hormone receptor, or GHr, a receptor that, when inhibited, reduces the level of circulating insulin-like growth factor-1, or IGF-1, produced in the liver. IGF-1 is a hormone that contributes to various diseases including acromegaly, which is characterized by abnormal growth of organs, face, hands and feet, as well as 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 completed pre-clinical toxicology studies on the compound and plans to begin clinical development for ATL1103 in 2011.

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

Excaliard reported the successful completion of three Phase 2 studies. In one Phase 2 study, treatment with EXC 001 produced a significant improvement in the appearance of scarring in patients who had revision surgery for excessive scarring. In another Phase 2 study, treatment with EXC 001 also reduced the severity of fine line scars and accelerated resolution of scarring compared to placebo. In a third Phase 2 study, treatment with EXC 001 produced a dose-dependent reduction in CTGF and inhibition of CTGF-induced collagen and other pro-fibrotic genes. In all three studies, Excaliard reported that treatment with EXC 001 produced statistically significant reductions in scar severity compared to placebo and EXC 001 was well tolerated with no important drug related adverse effects observed.

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 Therapeutics Inc., or iCo, for the treatment of various eye diseases that occur as complications of diabetes.

In May 2010, iCo and its investigators presented positive results from the Phase 1 study evaluating iCo-007 in patients with diffuse diabetic macular edema which showed that treatment with iCo-007 was well tolerated. In July 2010, iCo received approval to initiate a Phase 2 study on iCo-007 in patients with diabetic macular edema and plans to initiate Phase 2 studies of iCo-007 in 2011.

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 that we can meet FDA and European regulatory requirements for s afety 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, severe and rare/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 speci fically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Specifically, almost all of our antisense drugs in development cause a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target mRNA. The drug itself remains intact during this process, so it can remain active against additional target mRNA molecules and repeatedly trigger their degradation. Our antisense drugs can selectively bind to 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 antisen se 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 the planned advancement of our technology for future antisense drugs. In 2010, we selected our generation 2.5 chemistry, an advancement that we believe will increase the potency of our drugs and make oral administration commercially feasible. We expect that these generation 2.5 drugs will constitute some of our future drugs and serve as follow-on compounds to some of our current drugs in development.

Other Antisense Mechanisms

RNAi

In addition to advancing our RNase H mediated antisense drugs and core chemistries, we are also working to better understand the therapeutic utility of other antisense mechanisms, including RNA interference, or RNAi. For some of this research we work with satellite and partner companies, including Alnylam.

RNAi is an antisense mechanism that uses small interfering RNA, or siRNA, to target mRNA sequences. Most companies approach siRNA using double stranded oligonucleotides which exploit a cellular protein complex called the RNA-induced silencing complex, or RISC, to bind to the mRNA and to prevent the production of a disease-causing protein. We have a strong and growing intellectual property position in RNAi methodology and oligonucleotide chemistry for siRNA therapeutics. We have licensed these patents to Alnylam for double-stranded siRNA therapeutics.

At present, the double-stranded siRNA drugs in development by others are either administered locally or, if administered systemically require complex formulations to achieve sufficient delivery. We have recently identified the critical drug design elements required to achieve RNAi activity with a single stranded RNAi drug. We have also begun to chemically optimize these design elements to ensure that they survive long enough under physiological conditions to produce the desired activity in animals. As a result, we have created single stranded RNAi compounds that, when administered systemically, distribute in a manner similar to our second generation RNase H antisense drugs, without requiring the complex formulation or delivery vehicle typically necessary for double stranded RNAi oligonucleotides. These new single stranded RNAi drug designs are an exciting advance in RNAi technology.

Splicing

Splicing is a normal cellular mechanism that the cell uses to produce many different, but closely related proteins from a single gene by varying the processing of the RNA. Scientists estimate that because 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 can produce altered proteins that are involved in disease. In other cases, alternative splicing can omit 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 2009, we advanced into development our 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 splicin g 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, 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. F or 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 binds 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 modifica tions in exchange for equity, milestone payments and royalties on aptamer drugs Archemix develops using our technology.

Regulus Therapeutics

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-targeted 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 both companies' ownership. In early 2009, Regulus raised $20 million in a Series A preferred stock financing in which we and Alnylam were sole and equal investors in the financing. In October 2010, sanofi-aventis invested $10 million in Regulus, valuing Regulus at more than $130 million. From this investment sanofi-aventis acquired less than 10 percent ownership of Regulus, leaving us with 46 percent ownership. Alnylam owns the remaining equity. 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 currently provide Regulus with select general and administrative services under the terms of a services agreement and in accordance with an operating plan mutually agreed upon by us, Alnylam, and Regulus. As Regulus continues to mature, we will provide Regulus fewer services under the agreement.

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, as well as therapeutic uses of these microRNA compositions, and exclusive rights to Isis' and Alnylam's chemical modification intellectual property estates for microRNA applications. In total, Regulus' intellectual property portfolio includes early fundamental intellectual property in the field of microRNA, as well as over 900 filed patent applications pertaining to chemical modific ations of oligonucleotides for therapeutic applications, of which over 600 patents have been issued.

In April 2008, Regulus entered into a strategic alliance with GSK to discover, develop and commercialize microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and IBD, and in February 2010, Regulus and GSK expanded this alliance to include microRNA therapeutics targeting miR-122 for the treatment of hepatitis C virus infection, or HCV. This 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, including miR-122 for HCV. In May 2009, Regulus achieved the first milestone in this collaboration.

In June 2010, Regulus established a new collaboration with sanofi-aventis to discover, develop and commercialize microRNA therapeutics, initially focused on fibrosis. The alliance represents the largest microRNA partnership formed to date, valued at potentially over $750 million. As part of the agreement, sanofi-aventis retains an option to enter into a technology alliance worth up to $50 million to Regulus that could provide sanofi-aventis with access to Regulus' microRNA platform and a limited number of product licenses.

Beginning in the first quarter of 2010, as a result of a new accounting standard, we no longer included Regulus' revenue and operating expenses in our operating results and no longer included Regulus' cash which at December 31, 2009 was $30.7 million in our consolidated cash balance. 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 of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for characterizing diseases.

Regulus benefits from ours and Alnylam's microRNA research programs, which the companies combined to form Regulus. Regulus is addressing fundamental scientific questions regarding microRNAs and oligonucleotides and is utilizing this information to advance its platform technology and better understand the consequences of modulating microRNAs in tissues. Regulus also leverages its extensive network of leading academic collaborators to discover new microRNAs and support discovery efforts. Regulus combines leading biology with proprietary chemistry and bioinformatics to discover and develop microRNA therapeutics in key disease areas of high unmet medical need.

Regulus has a program for HCV, focused on targeting the microRNA, miR-122, which is now part of its 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 its alliance with GSK, Regulus has a research program in inflammation, where GSK has an option to license drugs developed from the program.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a development pipeline of 24 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 and developing 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. Many of the diseases we focus on present large market opportunities, where 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 to 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 have a strong history of establishing alliances with pharmaceutical industry leaders. These collaborations provide funding to advance our antisense drug discovery efforts and clinical development programs, and to continually enhance our technologies. 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 li censing.

GlaxoSmithKline

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

We received $40 million from GSK, including a $35 million upfront payment and a $5 million milestone payment. During 2010, we recognized revenue of $10.3 million from our relationship with GSK. We are also eligible to receive milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We are eligible to receive license fees and milestone payments, totaling up to nearly $1.5 billion, if all six programs are successfully developed for one or more indications and commercialized through pre-agreed sales targets. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

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 $125 million in funding for the development costs of mipomersen, which we expect to meet in 2011. Thereafter, we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the p rogram is profitable. As part of our alliance, Genzyme has a first right of negotiation for ISIS-SOD1$_{Rx}$.

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 two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

During 2010, 2009 and 2008, we recognized revenue of $66.9 million, $66.4 million and $48.2 million, respectively, primarily related to the upfront payments we received from Genzyme, which represented 62 percent, 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, our GCGR and GCCR programs. The collaboration ended and we regained the rights to drugs from both of these programs. We intend to move forward a more potent inhibitor for our GCGR program, which we identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program.

During 2009 and 2008, we recognized revenue of $18.4 million and $31.9 million, respectively, related to the $45 million upfront licensing fee, the $5 million milestone payment and the annual research and development funding under this collaboration, which represented 15 percent and 30 percent, respectively, of our total revenue for those years. During 2010, we did not recognize any revenue from our relationship with OMJP.

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. We finished amortizing the $15 million upfront fee into revenue when our period of performance under the original agreement ended in April 2010. Under the agreement, we will also receive up to $170 million for the achievement of pre-specified development and regulatory milestones for the first drug to reach the milestone, 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 collabo ration.

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. In March 2010, we earned a $6 million milestone payment from the initiation of clinical studies. In 2010, Bristol-Myers Squibb stopped the Phase 1 study of BMS-PCSK9$_{Rx}$ and discontinued development of the drug. In July 2010, we and Bristol-Myers Squibb extended our collaboration and license agreement by two years and will work together to discover a more potent PCSK9 antisense drug to move into development.

During 2010, 2009 and 2008, we recognized revenue of $12.2 million, $9.1 million and $12.0 million, respectively, related to the upfront licensing fee, milestone payment and the research funding from Bristol-Myers Squibb, which represented 11 percent, 8 percent and 11 percent, respectively, of our total revenue for those years.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. Eli Lilly and Company is responsible for the preclinical and clinical development of LY2181308. As of December 31, 2010, 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 we are continuing to develop the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development. However, if we publicly disclose the results from a Phase 2 clinical study of ISIS-EIF4E$_{Rx}$, and Eli Lilly and Company elects not to license ISIS-EIF4E$_{Rx}$ on the predefined terms, then we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2009 and 2008, we earned revenue from our relationship with Eli Lilly and Company totaling $75,000 and $156,000, respectively. During 2010, we did not recognize any revenue from our relationship with Eli Lilly and Company.

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. We refer to these companies as our drug discovery and development satellite companies, and this strategy as our satellite company strategy. Using this strategy we can create and support a much broader pipeline of drugs than we could develop on our own. 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.

The value of this strategy is evident in the broad pipeline of drugs we and our partners are developing to treat a large range of diseases. Using their resources and their expertise, our partners are instrumental in driving the development of antisense drugs that we discovered or co-discovered but fall outside our main areas of focus. For example, our satellite company partner, Altair, was developing an inhaled antisense drug, AIR645, we licensed to them for the treatment of asthma. We discovered AIR645 while evaluating targets involved in various inflammatory pathways. In our preclinical studies, AIR645 potently reduced target RNA and protein levels and demonstrated activity in mouse models of asthma. Altair evaluated AIR645 in patients with asthma in a Phase 2 study. In this study, treatment with AIR645 reduced its intended target and patients tolerated the drug well. However, reducing the target did not produce enough therapeutic benefit to warrant continued development, and Altair discontinued the program. While we were disappointed with these results, we gained significant insight from Altair’s efforts with our first inhaled antisense drug. We will use the information from the work that Altair conducted to inform our future efforts if we discover and develop additional inhaled antisense drugs.

Another example of our satellite company strategy is our partner Excaliard. Like Altair, Excaliard licensed a drug, EXC 001, from us. Excaliard advanced EXC 001 into clinical development and recently completed three Phase 2 studies. In these studies, local administration of EXC 001 significantly

reduced scar severity in patients. Excaliard intends to conduct additional clinical studies on EXC 001. We will benefit from the success of EXC 001 through our equity ownership, milestone payments and royalties on EXC 001. As with AIR645, we also gain information and experience by working closely with our satellite company partners in these disease areas. In summary, we believe that our satellite company strategy allows us to realize opportunities outside of our core focus while our committed and knowledgeable drug development partner incurs the cost of developm ent and assumes the risk.

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 IND for Achaogen's aminoglycoside drug, ACHN-490. In 2010, we received a $2 million milestone payment from Achaogen as a result of the initiation of a Phase 2 study of ACHN-490. At December 31, 2010 and 2009, we owned less than 10 percent o f Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug, we will receive milestone payments totaling up to $36.5 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 2010 and 2009, we recognized $2 million and $500,000, respectively, in revenue from our relationship with Achaogen, which does not include any revenue from the equity we received from Achaogen. During 2008, we did not recognize any revenue from our relationship with Achaogen.

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a biotechnology company that was focused 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. Altair evaluated AIR645 in patients with asthma in a Phase 2 study. In this study, treatment with AIR645 reduced its intended target and patients tolerated the drug well. However, reducing the target did not produce enough therapeutic benefit to warrant continued development and Altair discontinued the program. In December 2010, we and Altair terminated our collaboration and license agreement and we reacquired AIR645 as well as Altair's assets related to AIR645. Altair distributed cash to its preferred shareholders in December 2010, and we received $408,000 from that distribution. Our ownership of Altair was less than 10 percent at December 31, 2010 and 2009. During 2010, 2009 and 2008, we recognized revenue of $17,000, $79,000 and $207,000, 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 ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL1102 to Teva. ATL and Teva reported encouraging data from a Phase 2a study on ATL1102 in patients with relapsing and remitting MS. When Teva decided to continue the development of ATL1102, we earned $1.4 million of sublicense revenue, which we included in revenue in 2008. In 2009, we earned $2.0 million from Teva for manufacturing ATL1102 drug product. In March 2010, Teva terminated the licensing agreement for ATL1102 and returned to ATL rights to ATL1102.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. In December 2010, ATL completed a successful offering and raised approximately $2.4 million that it will use to advance ATL1103. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009 we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. Additionally, ATL will pay royalties to us on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

At December 31, 2010 and 2009, we owned less than 10 percent of ATL's equity. During 2010, we recorded revenue of $35,000 related to this collaboration compared to $401,000 and $1.6 million for 2009 and 2008, respectively.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of UC and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In September 2010, we participated in Atlantic Pharmaceuticals' financing by agreeing to sell to Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. At December 31, 2010 we owned approximately 12 percent of Atlantic Pharmaceuticals' equity compared with approximately 13 percent at D ecember 31, 2009. 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. In 2010, Atlantic Pharmaceuticals announced that in response to requests received from healthcare professionals, it was to supply alicaforsen under international Named Patient Supply regulations for patients with IBD. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

During 2010, 2009 and 2008, 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 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, 2010 and 2009, we owned less than 10 percent of Excaliard's equity and we have no remaining performance obligations.

In 2010 and 2011, we participated in Excaliard's financings at nominal amounts to maintain our ownership percentage. In addition, assuming Excaliard successfully develops and commercializes its first drug, we will receive milestone payments totaling up to $10.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs that Excaliard develops. We may also receive a portion of the fees Excaliard receives if it licenses drugs from our collaboration. During 2010, 2009 and 2008, we recognized revenue of $3,000, $290,000 and $384,000, 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 ea rned 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, iCo has 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 at a nominal amount to maintain our ownership percentage. As a result, our ownership in iCo was approximately 10 percent at December 31, 2009. In January 2010, 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 December 31, 2010 was approximately 12 percent. During 2010, 2009 and 2008 we recognized revenue of $7,000, $14,000 and $7,000, respectively, 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 December 2009, OncoGenex licensed OGX-011 to Teva for the treatment of multiple cancer indications for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in milestone payments OncoGenex may receive from Teva in addition to up to seven 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, 2010, OncoGenex had not achieved any milestone events 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 $4.2 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of the drug. As of December 31, 2010, OncoGenex had not achieved any milestone events related to OGX-427 but in January 2011, we earned a $750,000 milestone payment related to OncoGenex's phase 2 trial in men with metastatic prostate cancer.

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 $11.4 million in revenue from our relationship with OncoGenex. During 2010 and 2008, we did not recognize any revenue from our relationship with OncoGenex.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and is associated with a wide variety of conditions including infection, cancer and chronic inflammation. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In addition to license and option fees, we are eligible to receive development and commercial milestone payments and royalties on sales of drugs licensed to Xenon under the collaboration and a portion of sublicense revenue. If Xenon identifies a development candidate, Xenon may take an exclusive license for the development and worldwide commercialization for this development cand idate. During 2010, we did not recognize any revenue from our relationship with Xenon.

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 nominal 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 genera tes as well as milestone payments and royalties on Archemix' drugs that use our technology. During 2010 we recognized $25,000 in revenue from Archemix compared to $100,000 in 2009. 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. In December 2010, we earned a $375,000 milestone payment from Alnylam for the initiation of a Phase 1 study in their transthyretin, or TTR, program. We retained rights to a limited number of do uble-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam at the time of the agreement. During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million and a net gain on investments of $6.2 million. As of December 31, 2010, we no longer own any shares of Alnylam.

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, 2010, 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. Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million plus $2.6 million of research and development funding in 2009 and 2010. In November 2010, Alnylam terminated the ssRNAi research program and we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. As a result, any licenses to ssRNAi products 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, terminated. We continue to advance the development of ssRNAi technolo gy and during the course of the collaboration, we made improvements in the activity of ssRNAi compounds, including increased efficacy and potency as well as enhanced distribution.

As of December 31, 2010, we had earned a total of $37.1 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics that Alnylam has granted to pharmaceutical partners.

During 2010, 2009 and 2008, we generated revenue from our relationship with Alnylam totaling $10.3 million, $5.0 million and $4.6 million, respectively, representing nine percent, four percent and four percent, respectively, of our total revenue for those years.

AVI BioPharma, Inc., formerly Ercole Biotech, Inc.

In May 2003, we and Ercole entered an agreement where each party cross-licensed its respective intellectual property related to alternative RNA splicing. As part of the agreement, we granted Ercole an additional license to 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. During 2010, 2009 and 2008, 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 provided us 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 and 2008, we recognized revenue of $1.7 million and $2.7 million, respectively, from our relationship with CHDI. In 20 10, we did not recognize any revenue from our relationship with CHDI.

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 provided 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 believe our patent estate represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our pharmaceutical and satellite company partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies 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. To date, we have generated more than $398 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

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

Abbott Molecular Inc.

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

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is 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 may 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. Prior to 2010, we had assigned our rights to receive royalties for Macugen to Drug Royalty Trust 3. During 2009 and 2008, because of our agreement with Drug Royalty Trust 3, we did not recognize any revenue from our relationship with Eyetech. In 2010, we recognized $567,000 of revenue related to royalties for Macugen under our license to Eyetech.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. During 2010, 2009 and 2008, we recognized revenue of $1.8 million, $1.3 million and $1.2 million, respectively, from our relationship with Roche Molecular Systems.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense their technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of RNase H patents. In 2010 we recognized $20,000 in revenue from our relationship with Idera, compared to $10,000 in 2009. During 2008 we did not recognize any revenue from our relationship with Idera.

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 our second-generation chemistry. We expect these patents will expire in February 2013. Under the license, we paid IDT $4.9 million in license fees in 2001 and we will pay royalties on sales of any drugs utilizing the technology we licensed from IDT until the patents expire.

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay milestone payments to the University of Massachusetts totaling up to $650,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive from sublicensing its technology, and a royalty on sales of ISIS-SMN$_{Rx}$ in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

We have a license agreement with Verva under which we acquired an exclusive license to Verva's antisense patent rights related to ISIS-FGFR4$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology Verva licensed to us, we will pay milestone payments to Verva totaling up to $6.1 million for the achievement of key patent, clinical, and regulatory milestones. If we convert our license from an exclusive license to a nonexclusive license we could significantly reduce the milestone payments due to Verva. In addition, we will also pay royalties to Verva on sales of ISIS-FGFR4$_{Rx}$ if our product incorporates the technology we licensed from Verva.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $900,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive from sublicensing the Cold Spring Harbor Laboratory's technology, and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

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 both companies' ownership. In October 2010, sanofi-aventis invested $10 million in Regulus valuing Regulus at more than $130 million. From this investment sanofi-aventis acquired less than 10 percent ownership of Regulus, leaving us with 46 percent ownership. Alnylam owns the remaining outstanding preferred shares. 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.

sanofi-aventis

In June 2010, Regulus entered into a global, strategic alliance with sanofi-aventis to discover, develop, and commercialize microRNA therapeutics. The alliance includes $640 million of potential future milestone payments in addition to a $25 million upfront fee, a $10 million equity investment in Regulus that sanofi-aventis made in October 2010 and annual research support for three years with the option to extend two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. sanofi-aventis also received an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth up to an additional $50 million to Regulus. We and Alnylam are each eligible to receive 7.5 percent of the upfront payment and all potential milestone payments, in addition to royalties on product sales. As a result, in July 2010 we received a payment of $1.9 million representing 7.5 percent of the $25 million upfront fee from Regulus.

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 IBD, and in February 2010, Regulus and GSK expanded this alliance to include microRNA therapeutics targeting miR-122 for the treatment of HCV infection. 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, including miR-122 for HCV. 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 d rugs 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 $28 million in upfront payments from GSK, including $18 million in option fees and two $5 million notes. The notes 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 notes, and if the notes do not convert or if Regulus does not repay the notes by February 2013, we, Alnylam and Regulus may elect to repay the notes 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 pharmacolo gical 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 2010, 2009 and 2008, Regulus recognized revenue of $3.1 million, $3.0 million and $1.9 million, respectively, related to Regulus' collaboration with GSK.

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. In 2011, Genzyme plans to submit for marketing approval of mipomersen in the United States and Europe. If approved, the increased capacity of our manufacturing facility will provide the supply of drug substance we believe is necessary for the initial launch of mipomersen.

We rely on Genzyme to manufacture the finished drug product for mipomersen, including the initial launch supply. Genzyme has contracted with a contract manufacturing organization to prepare the finished vials of drug product for mipomersen, and plans to prepare the finished pre-filled syringes for mipomersen at one of its own manufacturing facilities. In addition, after the initial launch supply of drug substance for mipomersen, Genzyme will be responsible for the long-term supply of mipomersen drug substance and finished drug product.

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

As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for ATL, Bristol-Myers Squibb, Eli Lilly and Company, Genzyme, iCo, 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 can manufacture antisense drugs at commercially competitive prices.

Regulus Therapeutics

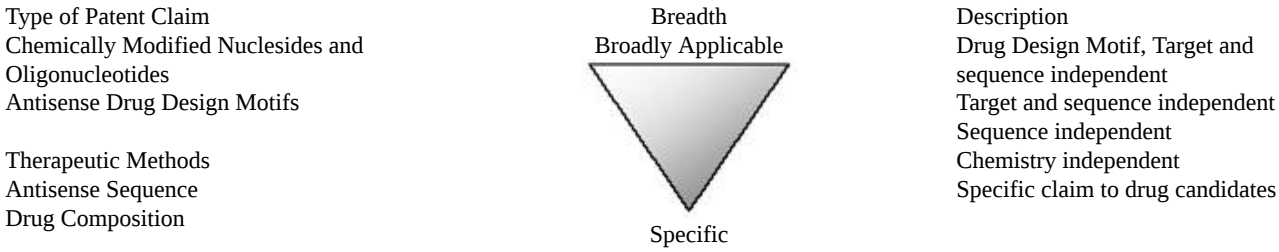
Currently, Regulus only requires small quantities of drugs to conduct its drug discovery programs. Regulus can satisfy current demand using its internal resources. When Regulus identifies a clinical candidate, it will have to ensure that it has a manufacturer for its drugs.

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 patent applications, as appropriate, to protect. As of February 14, 2011, we owned or exclusively licensed approximately 1,400 issued patents worldwide.

Isis Pharmaceuticals, Inc.

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



Chemically Modified Nucleosides and Oligonucleotides

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

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	5,914,396	2'-O-MODIFIED NUCLEOSIDES AND PHOSPHORAMIDITES	2016	Covers MOE nucleosides and oligonucleotides containing said nucleotides.
US	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'O-MODIFIED PURINES	2023	Covers certain MOE nucleosides and oligonucleotides containing said nucleotides.
US	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleoside analog and oligonucleotides containing these nucleoside analogs.
US	7,547,684	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleoside analog and oligonucleotides containing these nucleoside analogs.
US	7,666,854	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleoside analog and oligonucleotides containing these nucleoside analogs.

Antisense Drug Design Motifs

MOE Gapmers

Other Isis patents claim oligonucleotides comprising specific antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular antisense mechanism of action, such as RNase H, RNAi, or splicing. We have designed oligonucleotides incorporating motifs, which we refer to as chimeric compounds or gapmers to exploit the RNase H mechanism to achieve target RNA reduction. Almost all of our drugs, including mipomersen, contain this gapmer antisense drug design motif. In fact, we own a U.S. patent that covers each of our second generation antisense drugs until March of 2023. We have also successfully attained allowance of claims covering other gapmer drug designs, including our generation 2.2 drug designs which optimize gap size and overall length of the oligonucleotide. We have recently received a notice from the U.S. Patent and Trademark office allowing claims to methods of lowering a target RNA in an animal with a MOE gapmer composition having a gap of 12 to 18 DNA nucleotides. The following patents are some examples of our issued patents and allowed patent applications in this category:

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
US	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	Covers 2'-O-alkyl-O-alkyl gapmer oligonucleotides.
US	US2006/0063730	ENHANCED ANTISENSE OLIGONUCLEOTIDES	2025	Covers methods of lowering a target RNA in an animal with a MOE gapmer with a DNA gap of 12 to 18 nucletides.
EP	EP2021472 A1	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders

Bicyclic Nucleoside Gapmer Oligonucleotides

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

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
EP	EP2021472 A1	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, 10 to 14 nucleotides in length, with bicyclic nucleosides, which includes locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders
US	7,750,131	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers cEt containing gapmer compounds

Therapeutic Methods of Treatment and Antisense Drug Sequences

In addition to our broad core patents, we also own more than 900 patents, worldwide, with claims to antisense sequences and compounds directed to particular therapeutically important targets or methods of achieving clinical endpoints using these antisense compounds. Target patents may also include claims reciting the specific nucleic acid sequences utilized by our products, independent of chemical modifications and motifs. In addition, our product specific patents typically include claims combining specific nucleic acid sequences with nucleoside modifications and motifs. In this way, we seek patent claims narrowly tailored to protect our products specifically, in addition to the broader core antisense patents described above.

ApoB 100 and Mipomersen

In 2008, we obtained patent claims in the U.S. 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 the U.S. These issued claims should protect mipomersen from generic competition in the U.S. until at least 2024 and are listed in the following table:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
US	7,407,943	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Methods of inhibiting expression of apoB, decreasing serum cholesterol, decreasing lipoprotein levels, decreasing serum triglycerides, in a human with an antisense compound 12 to 30 nucleotide in length and 100% complementary to human apoB.
US	7,511,131	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2024	Antisense sequence and composition of matter of mipomersen.

RNAi Motifs and Mechanisms - The Crooke Patents

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

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

Manufacturing Patents

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

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 paten t 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

Our Drug Discovery and Development Business in General

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

Our products under development address numerous markets. The diseases 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, reimbursement and patent position.

Mipomersen

Genzyme plans to file a new drug application, or NDA, with the FDA in the United States and an MAA with the EMEA in Europe in 2011 for marketing approval for mipomersen. These filings will seek approval for the treatment of patients with homozygous FH in the United States and Europe. The European filing may also include patients with severe heFH. Maximally tolerated lipid-lowering therapies, including statins and apheresis, are the standard of care for these homozygous FH and severe heterozygous FH patients. Apheresis is a two to four hour process administered two to four times a month that mechanically separates LDL-C from the blood. Because apheresis is an invasive, time-consuming procedure conducted only in specialty centers, it can be difficult for patients to receive this treatment.

In addition, we expect that therapies currently in development may compete with mipomersen in this initial market. Excluding mipomersen, the most advanced therapy currently in development is Aegerion Pharmaceuticals' lomitapide, a small molecule drug that limits secretion of cholesterol and triglycerides from the intestines and the liver. Aegerion is initially developing lomitapide as an oral, once-a-day treatment for patients with homozygous FH. Aegerion is currently evaluating lomitapide in a Phase 3 study in 29 patients with homozygous FH. In earlier studies evaluating lomitapide, patients discontinued use of lomitapide at a high rate due to gastrointestinal adverse events, such as diarrhea, nausea and vomiting. In addition, some patients experienced elevations in liver enzymes and increased mean levels of fat in the liver, or hepatic fat, both of which Aegerion states it has observed in its ongoing Phase 3 clinical trial of lomitapide. Aegerion also states that patients in its ongoing Phase 3 trial have also experienced adverse gastrointestinal events. Aegerion states that before they submit an NDA for lomitapide to the FDA in 2011 they must complete additional studies to assess various other aspects of lomitapide. Aegerion plans to follow with an MAA submission in Europe in 2012.

We believe that the overall profile of mipomersen provides significant competitive advantage over potential competitors. In our clinical experience with mipomersen, we have seen substantial reductions in LDL-C as well as reductions in other atherogenic lipids linked to cardiovascular disease, including apoB, Lp(a), triglycerides and VLDL. In our Phase 3 studies that evaluated mipomersen in more than 250 patients, the most commonly observed adverse events were injection site reactions and flu-like symptoms. We also observed elevations in liver transaminases and moderate median increases in liver fat that appeared to be associated with greater reductions in LDL-C. We believe that this safety profile supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. Mipomersen is administered by injection once weekly while lom itapide is administered orally once daily. If mipomersen's product profile is not advantageous when compared to an oral drug, some patients may prefer the oral drug over mipomersen. Factors affecting a product's profile may include, efficacy, side effects, pricing and reimbursement.

In addition, our partner, Genzyme, has extensive experience in bringing medicines to patients with severe and rare diseases with an existing global commercial infrastructure in the cardiovascular community in Europe. In the United States, Genzyme also intends to capitalize on its existing sales and marketing infrastructure within specialized medical communities. Aegerion has no commercial partner for lomitapide and Aegerion has stated that it will need to build its own sales, marketing and commercial infrastructure.

Employees

As of February 14, 2011, we employed approximately 270 people in all of our functions, excluding manufacturing and operations which employed approximately 50 people. In addition, our Regulus subsidiary employed approximately 50 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 9, 2011:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D	65	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D	55	Director, Chief Operating Officer, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D	54	Senior Vice President, Antisense Research
Richard S. Geary, Ph.D	53	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 LLP, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations.

C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

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

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

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

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, including mipomersen, we cannot sell them.

We cannot guarantee that any of our drugs, including mipomersen, will be safe and effective, or will be approved for commercialization. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including mipomersen,

before a drug can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen. Even though we have completed the Phase 3 program to support our initial market for mipomersen, and Genzyme plans to file for marketing approval for mipomersen in Europe in the first half of 2011 and in the United States in 2011, it is possible that regulatory agencies will not approve mipomersen for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including mipomersen, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay commercialization of the drug.

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

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs, including mipomersen, are safe and effective 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. Similar results could occur with any additional clinical studies for mipomersen and in clinical studies for our other drugs. If any of our drugs in clinical studies, including mipomersen, does not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

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

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for mipomersen and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of mipomersen. 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 in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

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

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

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. Even if approved, we may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including mipomersen. The FDA has the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. If approved, the FDA may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time c onsuming to fulfill. In addition, if we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we may lose regulatory approval, or we may need to conduct additional clinical studies and/or change the labeling of our drug products including mipomersen.

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

If mipomersen or our other drugs is approved for marketing, our success will depend upon the medical community, patients and third-party payors accepting our drug as medically useful, cost-effective and safe. Even if the FDA or foreign regulatory agencies approve mipomersen or our other drugs for commercialization, doctors may not use our drugs to treat patients. For example, we currently have one commercially approved drug, Vitravene, a treatment for CMV retinitis in AIDS patients, which our partner is no longer marketing due to a dramatic decline in the incidence of CMV retinitis in AIDS patients. We and our partners may not successfully commercialize additional drugs.

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

The degree of market acceptance for mipomersen, and any of our other drugs, 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/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price that we receive for mipomersen or our other drugs or increase patient coinsurance to a level that makes mipomersen or our other drugs unaffordable.

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

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

We entered into this collaboration primarily to:

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

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize mipomersen, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain marketing approvals for and successfully commercialize mipomersen. Our collaboration with Genzyme may not continue or result in the successful commercialization of mipomersen. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing mipomersen, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for mipomersen. If Genzyme does not successfully commercialize mipomersen, we may receive limited or no revenues for mipomersen. In addition, sanofi-aventis and Genzyme announced they have entered into a definitive agreement under which sanofi-aventis is to acquire Genzyme. If sanofi-aventis or another company acquired Genzyme, Genzyme could be disrupted or distracted from performing its obligations under our collaboration.

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

We believe that our manufacturing facility has sufficient capacity to supply the drug substance necessary for the initial commercial launch of mipomersen, if approved. However, we rely on Genzyme to manufacture the finished drug product for mipomersen, including the initial commercial launch supply. In addition, if approved, Genzyme will be responsible for the long term supply of both mipomersen drug substance and finished drug product. Genzyme may not be able to reliably manufacture mipomersen drug substance and drug product to support mipomersen's long term commercialization. If Genzyme cannot reliably manufacture mipomersen drug substance and drug product, mipomersen may not achieve or maintain commercial success, which will harm our ability to generate revenue.

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

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

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

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

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

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

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

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

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

Regarding mipomersen, some competitors are pursuing a development strategy that competes with our strategy for mipomersen. Other companies are currently developing products that could compete with mipomersen. For example, products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing could potentially compete with mipomersen. For example, Aegerion is currently evaluating its MTP inhibitor in a Phase 3 study in homozygous FH patients. Our revenues and financial position will suffer if mipomersen receives regulatory approval, but cannot compete effectively in the marketplace.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical studies for mipomersen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including 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 drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2010, we had an accumulated deficit of approximately $756.7 million and stockholders' equity of approximately $244.5 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 have had only one product, Vitravene, approved for commercial use, but our exclusive distribution partner for this product no longer markets this product. We may incur additional o perating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

Our corporate partners are developing and/or funding many of the drugs in our development pipeline, including ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, Genzyme, GSK, OncoGenex, and Teva. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

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

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

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

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

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

For example, a collaborator such as Genzyme, GSK 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 drug that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for its own drugs.

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

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones for approval of mipomersen, 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 HoFH. The FDA required us to include data from two preclinical studies for carcinogenicity in the HoFH filing, which studies we have now completed. The FDA also indicated that for broader indications in high risk, high cholesterol patients the FDA would require an outcome study period for approval. This FDA guidance caused us to revise our development plans and timelines such that Genzyme's initial regulatory filings for mipomersen will seek marketing approval for the treatment of patients with HoFH in Europe in the first half of 2011and in the United States in 2011. The European filing may also include patients with severe hete rozygous familial hypercholesterolemia.

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

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

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

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 need 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 EPO Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds. Prior to its reinstatement, several parties originally opposed this patent and the EPO Opposition Division revoked it 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, which may be costly and which may not be resolved in our favor.

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

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. As of December 31, 2010, we had cash, cash equivalents and short-term investments equal to $472.4 million. If we do not meet our goals to commercialize mipomersen or our other drugs, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we 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 or drugs.

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2010, the market price of our common stock ranged from $7.59 to $11.82 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. 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 types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. In the event our losses exceed our insurance coverage, our financial condition would be adversely affected.

We depend on Regulus for development of our microRNA technology.

Regulus is a jointly owned company that we and Alnylam established to focus on discovery, developing, and commercializing of microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company, 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. However, Regulus and its employees are ultimately responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and 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 66²¤₃ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. Our stockholders' rights plan expired in December 2010. 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 a bility 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 agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

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 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 continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the economic crisis 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 ma y not continue to be available to us on acceptable terms, or at all.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Drug Discovery and Development

As of February 14, 2011, we occupied approximately 154,000 square feet of laboratory and office space in four buildings in Carlsbad, California, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. 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 2031 and has four five-year options to extend the lease.

In 2010, we entered into a lease agreement to construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility, except that we will not relocate our manufacturing operations. Our rent, which we will begin paying on January 1, 2012, is based on a percentage of the total construction costs. Once the new facility is complete, we will be responsible for the costs associated with maintaining the facility. Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs of the new facility less rent pa yments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

To support the expansion of our manufacturing activities due to the growing number of our antisense drug development partners and the clinical successes of our antisense drugs, including mipomersen, we entered into a lease agreement in 2010 to lease 25,792 square feet of laboratory and office space adjacent to our manufacturing facility. We are in the process of renovating the facility and preparing it for its intended use. When we occupy the facility, we will use it for laboratory and office space and to provide additional storage for our manufacturing materials. The lease has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods.

Regulus Therapeutics

As of February 14, 2011, Regulus occupied 21,470 square feet of laboratory and office space in San Diego, California. Regulus leases this facility under a lease agreement that expires in May 2017 and has two three-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 Bru ker. Discovery remains in its early stage. As such, we had no basis on which to predict or record a loss related to this claim as of December 31, 2010. We will continue to represent and defend Ibis 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

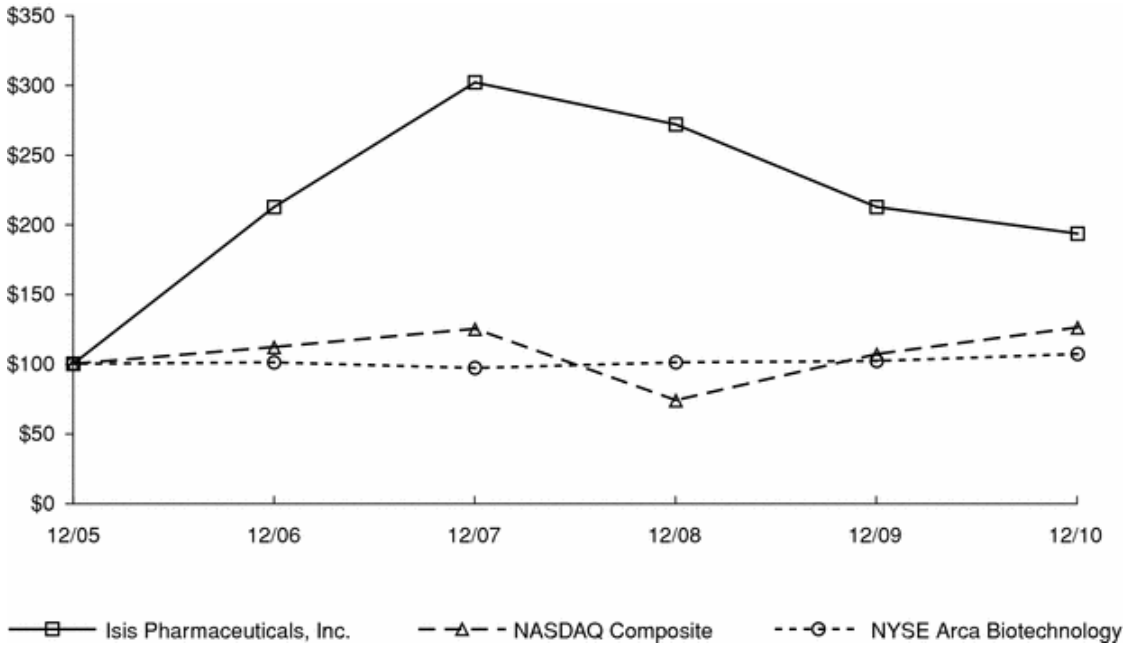
Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol “ISIS.” The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by The Nasdaq Global Select Market. These prices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

	HIGH	LOW
2010		
First Quarter	$ 11.82	$ 8.59
Second Quarter	$ 11.27	$ 8.46
Third Quarter	$ 10.19	$ 7.59
Fourth Quarter	$ 10.63	$ 7.86
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

As of February 23, 2011, there were approximately 836 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, 2005 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-05	Dec-06	Dec-07	Dec-08	Dec-09	Dec-10
Isis Pharmaceuticals, Inc.	$ 100	$ 212	$ 301	$ 271	$ 212	$ 193
NASDAQ Composite Index	$ 100	$ 112	$ 125	$ 74	$ 107	$ 126
NYSE Arca Biotechnology Index	$ 100	$ 101	$ 97	$ 101	$ 102	$ 107

(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,				
	2010	2009	2008	2007	2006
Consolidated Statement of Operations Data:					
Revenue(1)(7)	$ 108,473	$ 121,600	$ 107,190	$ 58,344	$ 14,859
Research and development expenses(1)(7)	$ 145,160	$ 134,623	$ 106,439	$ 78,204	$ 69,411
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)(2)(3)	$ (61,251)	$ (30,562)	$ (9,785)	$ (10,264)	$ (43,003)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(2)(3)	$ (61,251)	$ 155,066	$ (18,172)	$ (141,604)	$ (45,903)
Basic and diluted net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders(1)(2)(3)	$ (0.62)	$ (0.31)	$ (0.10)	$ (0.12)	$ (0.58)
Basic and diluted net income (loss) per share attributable to Isis Pharmaceuticals, Inc. common stockholders(2)	$ (0.62)	$ 1.58	$ (0.19)	$ (1.69)	$ (0.62)

(3)					
Shares used in computing basic and diluted net income (loss) per share	99,143	98,109	94,566	83,739	74,308

	As of December 31,				
	2010	2009	2008	2007	2006
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments(4)(6)	$ 472,353	$ 574,312	$ 490,998	$ 193,719	$ 193,333
Working capital(4)(6)	$ 377,247	$ 484,682	$ 393,685	$ 147,669	$ 181,064
Total assets(5)(6)	$ 550,477	$ 657,184	$ 572,776	$ 257,216	$ 255,907
Long-term debt and other obligations, less current portion(4)(5)(6)	$ 199,175	$ 243,675	$ 300,697	$ 135,426	$ 132,866
Accumulated deficit(5)(6)	$ (756,687)	$ (696,150)	$ (851,216)	$ (833,044)	$ (816,751)
Noncontrolling interest in Symphony GenIsis, Inc.	$ —	$ —	$ —	$ —	$ 29,339
Noncontrolling interest in Regulus Therapeutics Inc.(6)	$ —	$ 10,343	$ 4,737	$ 9,371	$ —
Noncontrolling interest in Ibis Biosciences, Inc.	$ —	$ —	$ 32,419	$ —	$ —
Investment in Regulus Therapeutics Inc.(6)	$ 870	—	$ —	$ —	$ —
Stockholders' equity(5)	$ 244,542	$ 302,065	$ 147,380	$ 59,585	$ 97,902

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

(2) 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 charge of $125.3 million related to excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc. in 2007.

(3) 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.

(4) 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.

(5) 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.

(6) Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we changed the way we account for our variable interest in Regulus. We adopted the new standard on a prospective basis; therefore, beginning in the first quarter of 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. We no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results o n a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 2, *Investment in Regulus Therapeutics Inc.*

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

Overview

We are the leading company in antisense 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 clinical value inflection points. In this way, our organization remains small and focused. We discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality p artners with late-stage development, commercialization and marketing expertise such as Bristol-Myers Squibb, Genzyme, GSK and Eli Lilly and Company. We also work with a consortium of smaller companies that can exploit our technology outside our primary areas of focus using 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 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 such as through collaborations with Achaogen and Archemix. Beyond human therapeutics, we benefit from the commercialization of products incorporating our technology by other companies that are better positioned to maximize the commercial potential of these inventions, such as when we sold our subsidiary Ibis Biosciences to AMI. All of these different types of relationships are part of our unique business model and create current and future shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. As an innovator in RNA-based drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, 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 $398 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. We and Genzyme reported positive data from four Phase 3 studies demonstrating consistent and robust lowering of LDL-C and other atherogenic lipids. Across these four studies, treatment with mipomersen reduced LDL-C in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. Mipomersen also reduced many other atherogenic lipids, including triglycerides, Lp(a), and non HDL-C lipids due to its unique mechanism of action. We believe the safety profile of mipomersen supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. The mipomersen data from all four of our Phase 3 studies support the profile of the drug as a novel tre atment to reduce LDL-C in patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

Our clinical experience with mipomersen demonstrates that antisense drugs work in man. 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. Over the past couple of years, we and our partners have reported positive data from five Phase 2 studies and seven Phase 1 studies. For example, we reported data from a positive Phase 2 study from our 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 characteristics create an encouraging profile for a new therapy to treat type 2 diabetics. Many of our partnered drugs are also showing encouraging activity in numerous diseases. Our partner Excaliard Pharmaceuticals reported data from three Phase 2 studies showing that treatment with EXC 001, a locally administered antisense drug, significantly reduced scarring in patients. 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 $830 million in payments from licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our currently partnered programs we have the potential to earn more than $3.5 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 as well as our inventive and focused research and development capabilities.

Business 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. 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 canc er. We currently have 24 drugs in development. Our partners are developing, with our support, 11 of these 24 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 characterizing diseases.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we changed the way we account for our variable interest in Regulus. We no longer include Regulus' revenue and operating expenses in our operating results and no longer include Regulus' cash, which at December 31, 2009 was $30.7 million in our consolidated cash balance. See Note 1, *Organization and Significant Accounting Policies*, and Note 2, *Investment in Regulus Therapeutics Inc.*, in the Notes to the Consolidated Financial Statements for a more detailed explanation of this change.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with 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 one may expect, 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:

- Assessing the propriety of revenue recognition and associated deferred revenue;

- Determining the proper valuation of investments in available-for-sale securities and other equity investments;
- Estimating to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the proper valuation of inventory;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities;
- Determining the fair value of convertible debt without the conversion feature; and
- Estimating 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 often can bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. When we receive 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. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we must 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. 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. To date, we have not had to make material adjustments to our estimates. 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 collaboratio n 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. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue; except, when Alnylam terminated the ssRNAi research program in November 2010, we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term.

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. For example, in March 2010, we earned a $6 million milestone payment when Bristol-Myers Squibb initiated Phase 1 clinical trials for BMS-PCSK9$_{Rx}$ and in July 2010, we earned a $5 million miles tone payment from GSK for the identification of ISIS-GSK1$_{Rx}$ as a development candidate.

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 can determine a standalone value for the delivered element and fair value for the undelivered elements, 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. We accounted for this $100 million 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 8, *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 jointly owned subsidiary, which we began accounting for using the equity method in the first quarter of 2010. 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, except for Regulus, under the cost method of accounting because we own less than 20 perce nt and do not have significant influence in their operations. Most of the cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those cirumstances we record a full valuation allowance. 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 2010, we recognized a $713,000 loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen offset by a $408,000 gain we recognized when Altair distributed cash to its preferred shareholders in December 2010. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. See further discussion about our investments in these satellite companies in Note 8, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Valuation of Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and 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 $1.5 million, $696,000 and $1.9 million for the years ended December 31, 2010, 2009 and 2008, 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 m ethod. 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. We have had net losses since inception, except for 2009, and as a result, we have established a 100 percent valuation allowance for our net deferred tax asset. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to the valuation allowance.

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.

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 utilizing the effective interest method. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our consolidated financial statements. For additional information, see Note 5, *Long-Term Obligations and Commitments*, i n 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. We determine the carrying amount of the liability component by measuring the fair value of a similar debt instrument that does not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

Consolidation of Variable Interest Entities

On January 1, 2010, we adopted an accounting standard, which replaced 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 impacts 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. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam share equally the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus . We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. We no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 2, *Investment in Regulus Therapeutics Inc.*

Stock-Based Compensation

We utilize the Black-Scholes model and assumptions discussed in Note 6, *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 o ur history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use an average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model. The expected term of stock options granted represents the period of time that we expect them to be outstanding.

We estimate the expected term of options granted based on historical exercise patterns. We estimate forfeitures based on historical experience. There were no material changes to our estimated forfeitures for 2010, 2009 and 2008.

We account for stock options granted to non-employees, which consist primarily of options granted to consultants, by estimating their fair value. Until the stock option vests, 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, 2010, total unrecognized compensation cost related to non-vested stock-based compensation plans was $9.1 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 1.2 years.

Results of Operations

As a result of adopting the new accounting standard related to our investment in Regulus, we have presented our net share of Regulus' operating results on a separate line in our Statements of Operations called "Equity in net loss of Regulus Therapeutics Inc." for 2010, compared to the line-by-line consolidation for 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. We discuss Regulus' operating results in a separate section below.

As a result of selling Ibis to AMI, we consider Ibis' financial results discontinued operations. Accordingly, we have presented the operating results of Ibis for 2009 and 2008 in our financial statements separately as discontinued operations.

Years Ended December 31, 2010 and December 31, 2009

Revenue

Total revenue for the year ended December 31, 2010 was $108.5 million, compared to $121.6 million for 2009. 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. We recognized new revenue in 2010 in the form of an upfront fee from our new partnership with GSK, which we are amortizing through the first quarter of 2015, milestone payments from GSK, Bristol-Myers Squibb, and Achaogen, and sublicensing income from Regulus' collaboration with sanofi-aventis. Additionally, when Alnylam terminated the ssRNAi research program in November 2010, we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. Our revenue in 2010 decreased compared to 2009 principally because the amortization of the upfront fee from our Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, collaboration ended in the third quarter of 2009. In addition, revenue decreased by $3.0 million because we are no longer including Regulus' revenue in our 2010 revenue.

Collaborations with GSK and Genzyme 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.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2010 was $102.9 million, compared to $108.1 million for 2009. Although we recognized $13.4 million of revenue for the milestone payments we received in 2010, $5.3 million of amortization of revenue related to the upfront payment we received from GSK in 2010 and $4.9 million of additional revenue when Alnylam terminated the ssRNAi research program in 2010. Our revenue in 2010 compared to 2009 decreased, primarily because revenue from our collaboration with OMJP ended in the third quarter of 2009. Research and development revenue also decreased by $3.0 million because we are no longer including Regulus' revenue in our 2010 revenue.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2010 was $5.6 million, compared to $13.5 million for 2009. The decrease primarily related to the $10 million sublicensing revenue we earned from OncoGenex in the fourth quarter of 2009 when OncoGenex entered into a strategic alliance with Teva.

Operating Expenses

Operating expenses for the year ended December 31, 2010 were $156.8 million, compared to $149.1 million for 2009. The higher expenses in 2010 were primarily due to increased costs related to advancing mipomersen towards its initial regulatory filings for marketing approval planned for 2011, maturing and expanding our pipeline, and implementing generation 2.5 chemistry. The increase in costs were offset in part by an $11.7 million decrease because we are no longer including Regulus' operating expenses in our 2010 operating expenses.

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.

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

	Year Ended December 31,	
	2010	2009
Research and development expenses	$ 135,012	$ 123,646
Non-cash compensation expense related to stock options	10,148	10,977
Total research and development	$ 145,160	$ 134,623

For the year ended December 31, 2010, we incurred total research and development expenses of $135.0 million, compared to $123.6 million for 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen, maturing and expanding our pipeline, and implementing generation 2.5 chemistry. The increase in costs were offset in part by a $9.1 million decrease because we are no longer including Regulus' operating expenses in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

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 pipelines. 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,	
	2010	2009
Antisense drug discovery	$ 33,175	$ 27,535
Non-cash compensation expense related to stock options	2,941	3,067
Total antisense drug discovery	$ 36,116	$ 30,602

Antisense drug discovery costs were $33.2 million for the year ended December 31, 2010, compared to $27.5 million for 2009. Both amounts exclude non-cash compensation expense related to stock options. The higher expenses in 2010 were primarily due to our planned investment to expand our pipeline by adding three to five new drugs a year and additional spending to identify our generation 2.5 chemistry. These activities resulted in an increase in personnel, laboratory supplies and research services provided by third parties in 2010.

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,	
	2010	2009
Mipomersen	$ 25,807	$ 26,909
Other antisense development products	29,907	17,472
Development overhead costs	4,713	4,253
Non-cash compensation expense related to stock options	3,207	3,578
Total antisense drug development	$ 63,634	$ 52,212

Antisense drug development expenditures were $60.4 million for the year ended December 31, 2010 compared to $48.6 million for 2009. Both amounts exclude non-cash compensation expense related to stock options. We attribute the increase to an increase in other antisense development projects due to the expansion of our drug pipeline.

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, 11 of our 24 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility for mipomersen 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, which we anticipate reaching in 2011. 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,	
	2010	2009
Manufacturing and operations	$ 17,513	$ 14,415
Non-cash compensation expense related to stock options	1,425	1,440
Total manufacturing and operations	$ 18,938	$ 15,855

Manufacturing and operations expenses for the year ended December 31, 2010 were $17.5 million, compared to $14.4 million for 2009, both amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in personnel costs

and services provided by third parties to support our expanded clinical development programs including mipomersen and depreciation expense related to the upgrades made to our manufacturing facility to prepare to manufacture mipomersen for launch.

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,	
	2010	2009
Personnel costs	$ 8,153	$ 7,859
Occupancy	6,587	7,230
Depreciation and amortization	6,394	6,379
Insurance	922	903
Other	1,840	2,739
Non-cash compensation expense related to stock options	2,576	3,058
Total R&D support costs	$ 26,472	$ 28,168

R&D support costs for the year ended December 31, 2010 were $23.9 million, compared to $25.1 million for 2009, both amounts exclude non-cash compensation expense related to stock options. The decrease in expenses primarily relates to lease modification fees that we paid in September 2009. Other R&D support costs also decreased because we are no longer including Regulus' R&D support costs in our 2010 operating expenses. After we move into our new facility in 2011, we anticipate that our rent expense will moderately increase.

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,	
	2010	2009
General and administrative expenses	$ 9,658	$ 12,107
Non-cash compensation expense related to stock options	2,011	2,408
Total general and administrative	$ 11,669	$ 14,515

General and administrative expenses for the year ended December 31, 2010 were $9.7 million, compared to $12.1 million for 2009. The decrease primarily related to Regulus' general and administrative expenses of $2.5 million in 2009, which we are no longer including in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

Equity in Net Loss of Regulus Therapeutics Inc.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer include Regulus' revenue and operating expenses in our operating results. Instead we are presenting our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we consolidated Regulus' financial results on a line-by-line basis. See Note 1, *Organization and Significant Accounting Policies*, and Note 2, *Investment in Regulus Therapeutics Inc.*, in the Notes to the consolidated financial statements for a more detailed explanation of this change.

Our equity in net loss of Regulus for the year ended December 31, 2010 was $2.2 million. Our share of Regulus' 2010 net loss was offset by a $4.7 million gain we recorded in October 2010 to reflect an increase in the valuation of Regulus and the change in our ownership percentage due to the $10 million investment sanofi-aventis made in Regulus valuing Regulus at more than $130 million. We had the option to adopt the new accounting standard on a retrospective or prospective basis. We chose to adopt it prospectively, therefore we did not adjust our prior period results. If we had retrospectively adopted the new standard, our share of equity in net loss of Regulus for the year ended December 31, 2009 would have been $6.1 million, which includes $1.7 million in losses that would have been previously suspended. Under the equity method of accoun ting, we are required to suspend losses if the carrying amount of our investment in Regulus exceeds the amount of funding we are required to provide. We will suspend recording our portion of Regulus' loss if the carrying amount of our investment in Regulus exceeds the amount of Regulus' GSK Notes that we guaranteed, which was $5.3 million at December 31, 2010. The decrease in our equity in net loss of Regulus is primarily related to the gain we recognized in 2010 when sanofi-aventis made its investment offset by an increase in Regulus' 2010 operating expenses. We discuss expenses related to Regulus in a separate section below.

Investment Income

Investment income for the year ended December 31, 2010 totaled $3.4 million, compared to $6.4 million for 2009. The decrease in investment income was primarily due to a lower average return on our investments resulting from the current market conditions and a lower average cash balance.

Interest Expense

Interest expense for the year ended December 31, 2010 totaled $13.2 million and was slightly higher compared to $12.7 million for 2009.

Gain (Loss) on Investments, net

Net loss on investments for the year ended December 31, 2010 was $713,000, compared to a gain on investments of $2.1 million for 2009. The net loss on investments in 2010 consisted of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen, offset by a $408,000 gain we recognized when Altair distributed cash to its preferred shareholders in December 2010. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. The 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 was uncertain we recorded a full valuation allowance. See further discussion about our investment in Altair in Note 8, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

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 as part of our financial results from continuing operations of $3.2 million for the year ended December 31, 2009. In 2010 we recorded $92,000 of income tax expense related to our 2009 tax return.

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,	
	2010	2009
Net loss from continuing operations, including income tax expense	$ (61,251)	$ (34,956)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	4,394
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (61,251)	$ (30,562)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2010 was $61.3 million, compared to $30.6 million for 2009. The increase in our net loss from continuing operations was primarily due to the following:

- $29.6 million increase in our loss from operations, excluding Regulus, as described above;
- $2.1 million decrease in our share of Regulus' net loss;
- $3.0 million decrease in investment income; and
- $3.0 million decrease in gain (loss) on investments.

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, in 2009 was $185.6 million, and 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 loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the year ended December 31, 2010 was $61.3 million, compared to a net income of $155.1 million for 2009. Basic and diluted net loss per share for the year ended December 31, 2010 was $0.62 per share, compared to basic and diluted net income of $1.58 per share for 2009. Net income and net income per share in 2009 primarily consisted of the $185.6 million gain, net of tax, which we recognized when we sold Ibis to AMI in the first quarter of 2009.

Net Operating Loss Carryforward

At December 31, 2010, we had federal, California and foreign tax net operating loss carryforwards of approximately $402.0 million, $315.1 million and $1.1 million, respectively. We also had federal and California research credit carryforwards of approximately $38.2 million and $12.9 million, respectively. Our federal and California tax loss carryforwards expire at various dates starting in 2014, unless previously utilized. We can carry forward our foreign tax losses indefinitely and use them to offset future taxable income, provided there is no substantial change in ownership. Our net operating loss and tax credit carryforwards may be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership"

provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on th e benefits that may arise from our net operating loss and tax credit carryforwards.

Regulus Therapeutics

Regulus' revenue for the year ended December 31, 2010 was $8.6 million, compared to $3.0 million for 2009. The increase primarily relates to the amortization of the $25 million upfront payment Regulus received from sanofi-aventis in July 2010 and the $3 million upfront license fee Regulus received from GSK in February 2010 for its HCV alliance targeting miR-122. Regulus is amortizing the $25 million and $3 million upfront payments it received from sanofi-aventis and GSK ratably into revenue through June 2015 and April 2014, respectively, which represents the end of its performance obligations based on the research and development plans included in the agreements.

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

	Year Ended December 31,	
	2010	2009
Research and development expenses	$ 19,775	$ 9,147
General and administrative expenses	3,721	2,490
Non-cash compensation expense related to stock options	603	99
Total Regulus operating expenses	$ 24,099	$ 11,736

Operating expenses for Regulus were $23.5 million for the year ended December 31, 2010, compared to $11.6 million for 2009, both amounts exclude non-cash compensation expense related to stock options. The increase primarily relates to Regulus' continued efforts to build its team to support its internal microRNA programs, the efforts associated with its GSK collaboration, and

the $3.8 million of sublicense fees paid to us and Alnylam from Regulus' strategic alliance with sanofi-aventis. With the strategic alliances with GSK and sanofi-aventis, we anticipate that Regulus' expenses will increase going forward as Regulus advances its research and development activities.

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 significant increase in 2009 revenue over 2008 was primarily a result of 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.

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. Licensing and royalty revenue in 2009 was higher primarily due to 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 due to revenue from its collaboration with GSK.

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 built 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

Research and Development Expenses

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

For the year ended December 31, 2009, we incurred total research and development expenses, excluding stock compensation, of $123.6 million, compared to $95.9 million for 2008. We attribute the increase in expenses to the expansion of our clinical development programs, expenses for Regulus as it built 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

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, excluding non-cash compensation expense, were $27.5 million for the year ended December 31, 2009, compared to $20.3 million for 2008. The higher expenses in 2009 were primarily due to increased activity levels related to our planned investment to fill our pipeline, additional spending to enhance our platform technology and additional spending 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 for the years ended (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, excluding non-cash compensation expense, were $48.6 million for the year ended December 31, 2009 compared to $36.4 million for 2008. 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.

Manufacturing and Operations

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, excluding non-cash compensation expense, for the year ended December 31, 2009 were $14.4 million, compared to $11.4 million for 2008. 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 Phase 3 program for mipomersen.

R&D Support

The following table sets forth information on R&D support costs for the years ended (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, excluding non-cash compensation expense, for the year ended December 31, 2009 were $25.1 million, compared to $21.1 million for 2008. 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.

General and Administrative Expenses

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

General and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2009 were $12.1 million, compared to $11.1 million for 2008. 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

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $11.6 million for the year ended December 31, 2009 compared to $7.6 million in 2008. 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.

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 then 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 a new accounting standard related to our 2¾ percent 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 5, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

The increase in intere st 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. 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 was 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 a net loss from discontinued operations of $8.4 million for 2008.

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.

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, 2010, we have earned approximately $927.2 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, 2010, we have raised net proceeds of approximately $820.5 million from the sale of our equity securities and we have borrowed approximately $566.9 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2010, we had cash, cash equivalents and short-term investments of $472.4 million and stockholders' equity of $244.5 million. In comparison, we had cash, cash equivalents and short-term investments of $574.3 million and stockholders' equity of $302.1 million at December 31, 2009. At December 31, 2010, we had consolidated working capital of $377.2 million, compared to $484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in 2010 for our operations, including $7.3 million that we paid for 2009 income taxes. Our cash and working capital also decreased because we are no longer including Regulus' cash, which was $30.7 million at December 31, 2009, in our consolidated cash balance. See Note 1, *Organization and Significant Accounting Policies*, for a more detailed explanation of this change.

As of December 31, 2010, our debt and other obligations totaled $144.3 million, compared to $140.8 million at December 31, 2009. The increase primarily relates to an increase in the carrying value of our 2⅝ percent convertible notes due to $7.8 million of non-cash amortization of the debt discount we recorded in 2010. Also contributing to the increase was $4.7 million of additional draw downs on our equipment financing arrangement offset by $4.4 million of principal payments we made in 2010 on our equipment financing arrangement. Also offsetting the increase was the $5.3 million convertible promissory note and the $94 9,000 equipment financing arrangement on Regulus' balance sheet as of December 31, 2009, which we are no longer consolidating in our 2010 balance sheet. For additional information, see Note 5, *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, 2010. 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**
2⅝ percent Convertible Subordinated Notes (principal and interest payable)	$ 177.4	$ 4.3	$ 8.6	$ 164.5	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 10.0	$ 5.9	$ 4.1	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.5	$ 0.1	$ 0.1	$ 0.1	$ 1.2
Capital Leases	$ 0.9	$ 0.1	$ 0.4	$ 0.4	$ —
Operating Leases	$ 32.4	$ 3.5	$ 2.8	$ 2.7	$ 23.4
Total	$ 222.2	$ 13.9	$ 16.0	$ 167.7	$ 24.6

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have 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 can 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.

In October 2008, we entered into a loan agreement with RBS Capital Finance 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. In November 2010, we further amended the loan agreement to extend the draw down period to July 2011. Under the loan agreement, we and Regulus can borrow up to $18.4 million and $1.0 million, respectively, in principal to finance the purchase of equipment until the end of the draw down period. 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 agreeme nt 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. In 2010, we drew down an additional $4.7 million in principal under the loan agreement. As of December 31, 2010, we had drawn down $16.7 million in principal under this loan agreement at a weighted average interest rate of 6.31 percent. The carrying balance under this loan agreement at December 31, 2010 and 2009 was $9.4 million and $10.0 million, respectively.

In March 2010, we entered into a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed is constructing a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of December 31, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $154.8 million.

We also lease from BioMed an approximately 28,704 square foot facility that houses our manufacturing suites for our drug development business. In March 2010, we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2010 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 of the new agreements 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 issuing additional shares of our common stock, issuing debt

instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We 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 2010 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, 2010 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, 2010, 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, 2010.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2010, 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, 2010, 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 reaso nable 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, 2010, 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, 2010 and 2009, and the related statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2010 of Isis Pharmaceuticals, Inc. and our report dated February 28, 2011 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2011

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "ELECTION OF DIRECTORS", including in particular the information under "Nominating, Governance and Review Committee" and "Audit Committee," contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 28, 2011 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2011 Annual Meeting of Stockholders to be held on June 16, 2011.

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

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2010.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options		Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	7,053,248	$	10.59	5, 200,855(c)
Equity compensation plans not approved by stockholders(b)	2,757,255	$	13.95	—
Total	9,810,503	$	11.54	5,200,855

(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, 139,306 remained available for purchase under the ESPP as of December 31, 2010. 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, 2010, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 2,757,255 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 3,164,043 shares had been exercised under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the option holder's employment or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the outstanding st ock 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 "Independence of the Board of Directors" and "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accountant Fees and Services

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

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 71.

(b) Exhibits

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

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 28th day of February, 2011.

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)	February 28, 2011
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	February 28, 2011
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 28, 2011
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	February 28, 2011
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 28, 2011
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 28, 2011
/s/ JOHN C. REED, M.D. PH.D. John C. Reed, M.D., Ph.D.	Director	February 28, 2011
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 28, 2011

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	Stock Purchase Agreement between the Registrant and Genzyme Corporation dated January 7, 2008. (8)
4.4	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)
4.5	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein.(14)
4.6	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. (36)
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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(32)
10.7	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(9)
10.8	Amendment #1 to the Product Development and Commercialization Agreement between Regulus Therapeutics Inc. and Glaxo Group Limited dated February 24, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)
10.9	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(19)
10.10	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (12)
10.11	Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(30)

10.12	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(8)
10.13	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)
10.14	Exclusive License and Nonexclusive Option Agreement between Regulus Therapeutics Inc. and Glaxo Group Limited dated February 24, 2010 . Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)
10.15	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (22)
10.16	Lease Agreement between the Registrant and BMR-Gazelle Court LLC dated March 30, 2010 . Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)
10.17	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(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, as amended.(36)

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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (12)

10.22* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. (21)

10.23* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant 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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(16)

10.29 Second Amendment to Lease Agreement between the Registrant and BMR-2282 Faraday Avenue LLC dated March 30, 2010 . Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)

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 Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010 . Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)

10.34 Collaboration and License Agreement dated June 17, 2010 between sanofi-aventis and Regulus Therapeutics Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

10.35 First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009.(32)

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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(23)

10.38 Non-Exclusive Technology Alliance and Option Agreement dated June 17, 2010 between sanofi-aventis and Regulus Therapeutics Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

10.39 Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (7)

10.42 Research Agreement dated October 22, 2007 between the Registrant and CHDI, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(4)

10.43 Founding Investor Rights Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated January 1, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (6)

10.44 Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated January 1, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.(6)

10.45 Amendment No. 1 to Amended and Restated License Agreement between the Registrant and OncoGenex Technologies Inc. dated December 18, 2009.(32)

10.46	Amendment Number One to the Amended and Restated License and Collaboration Agreement dated June 10, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)
10.47	Amendment Number One to the Founding Investor Rights Agreement dated June 7, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. (34)
10.48	First Amendment to Collaboration Research and License Agreement dated July 27, 2010 between Bristol Myers Squibb Company and the Registrant. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (35)
10.49	Second Amendment to Loan Agreement dated November 15, 2010 between the Registrant and RBS Asset Finance, Inc.
14.1	Registrant's Code of Ethics and Business Conduct.(21)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.

24.1	Power of Attorney.(37)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)
101	The following financial statements from the Isis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2010, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of stockholders' equity, (iv) consolidated statements of cash flows, and (v) notes to consolidated financial statements (tagged as blocks of text).

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

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

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

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

(36) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2010 Annual Meeting of Stockholders, filed with the SEC on April 16, 2010, and incorporated herein by reference.

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

* 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, 2010 and 2009, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2010. 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, 2010 and 2009, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2010, in conformity with U.S. generally accepted accounting principles.

As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for variable interest entities as a result of the adoption of the amendments to the FASB Accounting Standards Codification resulting from Accounting Standards Update No. 2009-17, Consolidations (Topic 810): Improvements to Financial Reporting by Enterprises Involved with Variable Interest Entities, effective January 1, 2010.

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, 2010, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 28, 2011 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2011

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

	December 31, 2010	December 31, 2009
ASSETS		
Current assets:		
Cash and cash equivalents	$ 70,052	$ 105,255
Short-term investments	402,301	469,057
Contracts receivable	1,242	10,899
Inventories	2,484	2,768
Other current assets	7,058	8,147
Total current assets	483,137	596,126
Property, plant and equipment, net	35,703	27,338
Licenses, net	12,288	14,542
Patents, net	15,821	15,909
Deposits and other assets	3,528	3,269
Total assets	$ 550,477	$ 657,184
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,523	$ 4,696
Accrued compensation	6,831	7,135
Income taxes payable	—	7,323
Accrued liabilities	12,389	12,339
Current portion of long-term obligations	5,645	4,270
Current portion of deferred contract revenue	74,502	75,681
Total current liabilities	105,890	111,444
Long-term deferred contract revenue	50,413	107,097
$2^{5}/_{8}$ percent convertible subordinated notes	132,895	125,100
Long-term obligations, less current portion	5,720	11,478
Long-term financing obligation	10,147	—
Investment in Regulus Therapeutics Inc.	870	—
Total liabilities	305,935	355,119

Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 99,393,780 and 98,850,934 shares issued and outstanding at December 31, 2010 and 2009, respectively	99	99
Additional paid-in capital	1,000,181	985,620
Accumulated other comprehensive income	949	2,153
Accumulated deficit	(756,687)	(696,150)
Total Isis Pharmaceuticals, Inc. stockholders' equity	244,542	291,722
Noncontrolling interest in Regulus Therapeutics Inc.	—	10,343
Total stockholders' equity	244,542	302,065
Total liabilities and stockholders' equity	$ 550,477	$ 657,184

See accompanying notes.

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

	Years Ended December 31,		
	2010	2009	2008
Revenue:			
Research and development revenue under collaborative agreements	$ 102,921	$ 108,131	$ 98,853
Licensing and royalty revenue	5,552	13,469	8,337
Total revenue	108,473	121,600	107,190
Expenses:			
Research and development	145,160	134,623	106,439
General and administrative	11,669	14,515	13,811
Total operating expenses	156,829	149,138	120,250
Loss from operations	(48,356)	(27,538)	(13,060)
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	(2,228)	—	—
Investment income	3,370	6,361	11,318
Interest expense	(13,232)	(12,672)	(11,812)
Gain (loss) on investments, net	(713)	2,084	(965)
Loss from continuing operations, before income tax expense	(61,159)	(31,765)	(14,519)
Income tax expense	(92)	(3,191)	—
Net loss from continuing operations	(61,251)	(34,956)	(14,519)
Discontinued operations:			
Loss from discontinued operations	—	(29)	(8,387)
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)
Net income (loss)	(61,251)	150,672	(22,906)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	4,394	4,734
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (61,251)	$ 155,066	$ (18,172)
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.62)	$ (0.31)	$ (0.10)
Net income (loss) from discontinued operations	—	1.89	(0.09)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.62)	$ 1.58	$ (0.19)
Shares used in computing basic and diluted net income (loss) per share	99,143	98,109	94,566

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

Years Ended December 31, 2010, 2009 and 2008
(In thousands)

Description	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock Shares	Common stock Amount	Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Regulus	Ibis	Total stockholders' equity
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
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
Adoption of accounting standard to deconsolidate Regulus Therapeutics Inc.	—	—	(1,954)	—	714	(10,343)	—	(11,583)
Comprehensive loss:								
Net loss	—	—	—	—	(61,251)	—	—	(61,251)
Change in unrealized losses	—	—	—	(1,342)	—	—	—	(1,342)
Reclassification adjustment for realized losses included in net loss	—	—	—	138	—	—	—	138
Comprehensive loss								(62,455)
Options exercised and employee stock purchase plan issuances	475	—	4,356	—	—	—	—	4,356
Warrants exercised	68	—	—	—	—	—	—	—
Share-based compensation expense	—	—	12,159	—	—	—	—	12,159
Balance at December 31, 2010	99,394	$ 99	$ 1,000,181	$ 949	$ (756,687)	$ —	$ —	$ 244,542

See accompanying notes.

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

	Years Ended December 31, 2010	2009	2008
Operating activities:			
Net income (loss)	$ (61,251)	$ 150,672	$ (22,906)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Depreciation	4,840	3,935	2,868
Amortization of patents	1,961	3,024	1,610
Amortization of licenses	2,376	2,344	2,339
Amortization of premium (discount) on investments, net	5,075	2,026	(225)
Amortization of debt issuance costs	507	507	529
Amortization of 2 5/8 percent convertible subordinated notes discount	7,795	7,107	6,477
Share-based compensation expense	12,159	13,385	15,063
Equity in net loss of Regulus Therapeutics Inc.	2,228	—	—
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 from the sale of property, plant and equipment	(72)	—	—
(Gain) loss on investments, net	713	(2,084)	965
Non-cash losses related to patents, licensing and property, plant and equipment	1,512	696	1,877
Excess tax benefits on share-based compensation	—	(278)	—
Changes in operating assets and liabilities:			
Contracts receivable	10,479	(6,778)	1,238

Inventories	284	(17)	(1,323)
Other current and long-term assets	(943)	(955)	(2,657)
Accounts payable	1,325	(3,652)	962
Accrued compensation	394	(4,371)	(3,255)
Income taxes payable	(7,178)	(10,013)	—
Accrued liabilities	1,013	4,318	4,923
Deferred contract revenue	(46,810)	(82,650)	210,975
Net cash (used in) provided by operating activities	(63,593)	(108,441)	212,031
Investing activities:			
Purchases of short-term investments	(530,137)	(776,381)	(483,129)
Proceeds from the sale of short-term investments	577,533	578,886	265,951
Purchases of property, plant and equipment	(13,237)	(13,414)	(13,665)
Proceeds from the sale of property, plant and equipment	185	—	—
Proceeds from land sold to BioMed	10,147	—	—
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	(16,228)	—	—
Acquisition of licenses and other assets	(4,319)	(2,880)	(3,402)
Purchases of strategic investments, net of proceeds received	(250)	(1,349)	—
Proceeds from the sale of strategic investments	—	2,848	—
Net cash (used in) provided by investing activities	23,694	(212,290)	(234,245)
Financing activities:			
Net proceeds from issuance of equity	4,356	13,156	12,714
Excess tax benefits on share-based compensation	—	278	—
Proceeds from issuance of convertible promissory note to GlaxoSmithKline	—	—	5,000
Proceeds from equipment financing arrangement	4,694	6,394	7,048
Principal payments on debt and capital lease obligations	(4,354)	(2,827)	(7,239)
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
Net cash provided by financing activities	4,696	202,001	107,585
Net (decrease) increase in cash and cash equivalents	(35,203)	(118,730)	85,371
Cash and cash equivalents at beginning of year	105,255	223,985	138,614
Cash and cash equivalents (including cash and cash equivalents classified as assets from discontinued operations of $0, $0 and $6.1 million at December 31, 2010, 2009 and 2008, respectively) at end of year	$ 70,052	$ 105,255	$ 223,985
Supplemental disclosures of cash flow information:			
Interest paid	$ 4,889	$ 4,883	$ 4,607
Income taxes paid, net of refund received	$ 7,270	$ 13,205	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 922	$ 870	$ 2,873
Capital lease obligations	$ 770	$ —	$ —

See accompanying notes

ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. In addition to our wholly owned subsidiaries, our consolidated financial statements include our equity investment in Regulus Therapeutics Inc. (formerly Regulus Therapeutics LLC) , an entity we identified as a variable interest entity. Beginning in 2010, as a result of adopting a new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we concluded that we are no longer the primary beneficiary of Regulus. As such we have presented our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus The rapeutics Inc." On our consolidated balance sheet, we have presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we were the primary beneficiary of Regulus and as such we consolidated Regulus' financial results on a line-by-line basis. We have not reclassified amounts in the prior period financial statements to conform to the current year presentation.

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 2009 financial statements presentation. Prior to the sale of Ibis, we identified Ibis as a variable interest entity that we consolidated. We have eliminated in consolidation all significant intercompany balances and transactions.

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, 2010, 2009 and 2008, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would be anti-dilutive:

- $2^5/_8$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options;
- Warrants issued to Symphony GenIsis Holdings LLC; and
- Warrants issued for the 2005 Private Placement Financing

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 in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Research and development revenue under collaborative agreements

We often enter into collaborations under which we receive non-refundable upfront payments. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we must 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. We have made estimates of our continuing obligations on several agreements. To date, we have not had to make material adjustments to our estimates. 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 act ivities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue except, when Alnylam terminated the ssRNAi research program in November 2010, we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term.

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 standalone value for the delivered element and fair value for the undelivered elements, 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. 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 8, *Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

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

Research and development expenses

We expense research and development costs as we incur them. Included in research and development expenses are costs associated with our collaboration agreements. For the years ended December 31, 2010, 2009 and 2008, research and development costs of approximately $44.6 million, $57.1 million, and $45.0 million, respectively, were related to collaborative research and development arrangements.

Concentration of credit risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. We place our cash equivalents and certain of our short-term investments with reputable financial institutions. We 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 with an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's or Fitch, respectively. 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 jointly owned subsidiary, which we began accounting for using the equity method in the first quarter of 2010. 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, except for Regulus, under the cost method of accounting because we own less than 20 perce nt and do not have significant influence in their operations. Most of the cost method investments we hold are in early stage biotechnology companies and realization of our equity position in those companies is uncertain. In those cirumstances we record a full valuation allowance. 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.

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 m ethod. 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, 2010, 2009 and 2008. Total inventory, which consisted of raw materials, was $2.5 million and $2.8 million as of December 31, 2010 and 2009, respectively.

Property, plant and equipment

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

	December 31,	
	2010	2009
Equipment and computer software	$ 38,685	$ 37,098
Leasehold improvements	25,147	24,822
Furniture and fixtures	2,550	1,777
	66,382	63,697
Less accumulated depreciation	(40,826)	(36,359)
	25,556	27,338
Land	10,147	—
	$ 35,703	$ 27,338

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. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately three years and 15 years. The cost of our licenses at December 31, 2010 and 2009 was $36.2 million and $36.1 million, respectively. Accumulated amortization related to licenses was $23.9 million and $21.6 million at December 31, 2010 and 2009, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2011, 2012 and 2013 and $2.2 million for the years ending December 31, 2014 and 2015.

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 patents that we are not actively pursuing and write off any associated costs. We amortize patent costs over their estimated useful lives of 10 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 2.5 years and 2.9 years at December 31, 2010 and 2009, respectively. In 2010, 2009 and 2008, we recorded a non-cash charge of $1.5 million, $696,000 and $1.8 million, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values except i n 2008 when the charge primarily related to the assignment of patents to certain of our partners.

The cost of our patents at December 31, 2010 and 2009 was $33.3 million and $31.4 million, respectively. Accumulated amortization related to patents was $17.5 million and $15.5 million at December 31, 2010 and 2009, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)
2011	$ 1.7
2012	$ 1.2
2013	$ 0.8
2014	$ 0.6
2015	$ 0.5

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 $1.5 million, $696,000 and $1.9 million for the years ended December 31, 2010, 2009 and 2008, 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.

Equity method of accounting

On January 1, 2010, we adopted an accounting standard, which replaced 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 impacts 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. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share equally the ability to impact Regulus' economic performance, we are no longer the pri mary beneficiary of Regulus. We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. We no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 2, *Investment in Regulus Therapeutics Inc.*

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. For 2008, our consolidated financial statements included two variable interest entities, Regulus and Ibis, for which we were the primary beneficiary. As a result of adopting the new accounting standard related to our investment in Regulus in 2010, we deconsolidated Regulus because we are no longer the primary beneficiary of Regulus. See Note 2, *Investment in Regulus Therapeutics Inc.*, for addition al details. Prior to the sale of Ibis to AMI in January 2009, we identified Ibis as variable interest entity that we consolidated. See Note 3, *Discontinued Operations*, for additional details.

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 perio ds if actual forfeitures differ from those estimates.

We utilize the Black-Scholes model as our method of valuing 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 mo dels 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 consultants, by estimating their fair value. Until the stock option vests, 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 6, *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. 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, 2010, 2009 and 2008 in our Consolidated Statements of Stockholders' Equity.

Convertible debt

We account for our $2^5/_8$% convertible notes 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 $2^5/_8$% 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 utilizing the effective interest method. For additional information, see Note 5, *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.

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. To estimate the fair value of securities classified as Level 2, we utilize the services of various fixed income pricing providers that use an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids.

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, 2010 (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)	$ 68,618	$ 50,379	$ 18,239	$ —
Corporate debt securities (2)	244,228	—	244,228	—
Debt securities issued by U.S. government agencies (2)	127,041	—	127,041	—
Debt securities issued by the U.S. Treasury (2)	24,040	24,040	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	6,992	—	6,992	—
Equity securities (3)	2,011	2,011	—	—
Total	$ 472,930	$ 76,430	$ 396,500	$ —

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

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

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

Income Taxes

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

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

Impact of recently issued accounting standards

In October 2009, the FASB issued a new accounting standard for revenue arrangements with multiple deliverables. This new standard requires companies to separate multiple-deliverable arrangements if the delivered item has stand-alone value and at inception allocate arrangement consideration using a selling price hierarchy. The new standard also requires additional disclosures about multiple-deliverable arrangements. This guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010 and is effective for our fiscal year 2011. We do not expect this new standard to have a material impact on our financial statements.

In March 2010, the FASB issued a new accounting standard that establishes a revenue recognition method for milestone payments in research and development agreements. Under the new standard, entities can make an accounting policy election to recognize a payment that is contingent upon the achievement of a substantive milestone in its entirety in the period in which the entity achieves the milestone. We have historically applied a revenue recognition method for milestone payments that is consistent with this new standard. Therefore when we adopt this new standard in 2011, the only change required is to provide additional disclosures about the substantive nature of the milestone payments we are entitled to under our research and development agreements.

2. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics.

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 both companies' ownership. In October 2010, sanofi-aventis invested $10 million in Regulus. From this investment sanofi-aventis acquired less than 10 percent ownership of Regulus, leaving us with 46 percent ownership. Alnylam owns the remaining equity. 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 Regu lus decides not to develop either itself or with a partner.

Regulus Collaborations

sanofi-aventis

In June 2010, Regulus entered into a global, strategic alliance with sanofi-aventis to discover, develop, and commercialize microRNA therapeutics. The alliance includes $640 million of potential milestone payments in addition to a $25 million upfront fee, a $10 million equity investment in Regulus that sanofi-aventis made in October 2010 and annual research support for three years with the option to extend two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. sanofi-aventis also received an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth up to an additional $50 million to Regulus. We and Alnylam are each eligible to receive 7.5 percent of the upfront payment and all potential milestone payments, in addition to royalties on product sales. As a result, in July 2010 we received a payment of $1.9 million representing 7.5 percent of the $25 million upfront fee from Regulus.

GlaxoSmithKline

In April 2008, Regulus entered into a strategic alliance with GlaxoSmithKline, or GSK, to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, or IBD, and in February 2010, Regulus and GSK expanded this alliance to include microRNA therapeutics targeting microRNA 122, or miR-122, for the treatment of hepatitis C virus infection, or HCV. 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, including miR-122 for HCV. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exer cise 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 $28 million in upfront payments from GSK, including $18 million in option fees and two $5 million notes. The notes 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 notes, and if the notes do not convert or if Regulus does not repay the notes by February 2013, 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 pharmacolog ical 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.

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.

Equity method of accounting

On January 1, 2010, as a result of adopting the new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we prospectively changed the way we account for our variable interest in Regulus. Since we and Alnylam share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. Beginning in 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Below is a table summarizing the accounting impact to our balance sheet as of January 1, 2010 as a result of adopting the equity method of accounting (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Total Assets	$ 657,184	$ 626,006	$ (31,178)
Total Liabilities	$ 355,119	$ 335,524	$ (19,595)
Total Stockholders' Equity	$ 302,065	$ 290,482	$ (11,583)

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

Under the equity method of accounting, we are required to suspend recognizing losses if the carrying amount of our investment in Regulus exceeds the amount of funding we are required to provide to Regulus. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GSK, we will continue to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.3 million at December 31, 2010. If we had been applying the equity method from inception, we would have suspended recognizing our share of Regulus' losses in 2008 because it would have exceeded the amount we guaranteed under the first GSK convertible note. When we made the $10 million investment in March 2009, we would have recognized all of the suspended losses.

3. Discontinued Operations

In January 2009, AMI completed its acquisition of Ibis for a total purchase price of $215 million. Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation. Accordingly, we have presented the operating results of Ibis in our consolidated statements of operations as discontinued operations. 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 years ended December 31, 2009 and 2008 are as follows (in thousands):

	Year Ended December 31,	
	2009	2008
Revenue	$ —	$ 12,586
Total operating expenses	35	28,393
Loss from operations	(35)	(15,807)
Other income, net	—	5,317
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6	2,103
Loss from discontinued operations	(29)	(8,387)
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)

We do not have any remaining assets and liabilities from discontinued operations in our accompanying consolidated balance sheets at December 31, 2010 and 2009. We have not separately classified cash flows from discontinued operations in our consolidated statement of cash flows.

4. Investments

As of December 31, 2010, 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 with an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2010:

One year or less	86%
After one year but within five years	14%
Total	100%

At December 31, 2010, 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 (formerly Pantheco A/S), Achaogen, Atlantic Pharmaceuticals Limited, Altair and Excaliard, which are privately-held and ATL and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the

cost method of accounting. During 2010, we recognized a $713,000 loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen offset by a $408,000 gain we recognized when Altair distributed cash to its preferred shareholders in December 2010. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. See further discussion about our investments in these satellite companies in Note 8, *Collaborative Arrangements and Licensing Agreements*.

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

December 31, 2010	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 196,010	$ 294	$ (41)	$ —	$ 196,263
Debt securities issued by U.S. government agencies	119,890	53	(34)	—	119,909
Debt securities issued by the U.S. Treasury	24,030	10	—	—	24,040
Debt securities issued by states of the United States and political subdivisions of the states	6,989	3	—	—	6,992
Total securities with a maturity of one year or less	346,919	360	(75)	—	347,204
Corporate debt securities	47,842	167	(44)	—	47,965
Debt securities issued by U.S. government agencies	7,139	4	(11)	—	7,132
Total securities with a maturity of more than one year	54,981	171	(55)	—	55,097
Subtotal	$ 401,900	$ 531	$ (130)	$ —	$ 402,301
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,353	$ —	$ (880)	$ 2,011
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,353	$ —	$ (880)	$ 2,636
	$ 404,063	$ 1,884	$ (130)	$ (880)	$ 404,937

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

Investments we consider to be temporarily impaired at December 31, 2010 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses
Corporate debt securities	25	$ 58,438	$ (85)
Debt securities issued by U.S. government agencies	13	48,370	(45)
Total temporarily impaired securities	38	$ 106,808	$ (130)

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.

5. Long-Term Obligations and Commitments

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

	December 31,

	2010	2009
2 5/8 percent convertible subordinated notes	$ 132,895	$ 125,100
Equipment financing arrangement	9,440	10,046
Leases and other obligations	1,925	360
GlaxoSmithKline convertible promissory note, including accrued interest	—	5,342
Total	$ 144,260	$ 140,848
Less: current portion	(5,645)	(4,270)
Total Long-Term Obligations	$ 138,615	$ 136,578

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 in cash 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, 2010, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value based on quoted market prices was $162.3 million. 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. We did not include the effect of the conversion of the note into our common stock in the computation of diluted net 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 2009, we began accounting for the 2 5/8 percent notes using an 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 of adopting the standard, interest expense for the year ended December 31, 2010, 2009 and 2008 included $7.5 million, $6.8 million and $6.2 million 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. In November 2010, we amended the loan agreement to extend the draw down period to July 2011. Under the loan agreement, we could borrow up to $18.4 million in principal to finance the purchase of equipment until the end of the draw down period. In addition, in 2009 Regulus borrowed $1 million to finance the purchase of its equipment. 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 four percent. We are usin g the equipment purchased under the loan agreement as collateral. In 2010, we drew down an additional $4.7 million in principal under the loan agreement. As of December 31, 2010, we had drawn down $16.7 million in principal under this loan agreement at a weighted average interest rate of 6.31 percent. The carrying balance under this loan agreement at December 31, 2010 and 2009 was $9.4 million and $10.0 million, respectively.

Capital Lease

In 2010, we entered into a lease agreement associated with the purchase of certain office equipment. Since the lease contains a bargain purchase option, we classified it as a capital lease. At December 31, 2010, we had approximately $773,000 outstanding under the lease. The lease bears interest at a rate of 5.14 percent and has a term of five years. The office equipment related to this capital lease is included in our property, plant and equipment. At December 31, 2010, this equipment had a net book value of $705,000, which included $65,000 of accumulated depreciation.

GlaxoSmithKline Convertible Promissory Note

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. 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 and Alnylam 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 computatio n of diluted net income (loss) from continuing operations per share because the effect would have been anti-dilutive.

As a result of adopting the new accounting standard related to our investment in Regulus in 2010, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." compared to the line-by-line consolidation in 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. See Note 2, *Investment in Regulus Therapeutics Inc.*, for additional details.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2010 are as follows (in thousands):

2011	$	10,406
2012		7,354
2013		5,740
2014		164,878
2015		230
Thereafter		1,200
Subtotal	$	189,808
Less: current portion		(5,645)
Less: fixed and determinable interest		(16,736)
Less: debt discount		(29,605)
Deferred rent		793
Total	$	138,615

Operating Leases

We lease certain office equipment as well as office and laboratory space under non-cancelable operating leases with terms through December 2031. We currently occupy approximately 154,000 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. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered into a lease agreement with an affiliate of BioMed Realty, L.P. (“BioMed”). Under the lease, BioMed is constructing a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with maintaining the facility. Since our rent is based on a percentage of total construction costs spent by B ioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of December 31, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $154.8 million.

Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs spent by BioMed to acquire the land and build the new facility less rent payments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

In conjunction with the new lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed, who will construct the new facility on it. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land, which requires us to account for the purchase and sale of the land as a financing transaction. As such, our property, plant and equipment at December 31, 2010 included the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease terminates.

In connection with the sale of our 28,704 square foot manufacturing facility in 2005, we leased back the facility from BioMed for 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. In connection with the lease, we executed a stand by letter of credit for $500,000. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

To support the expansion of our manufacturing activities due to the growing number of our antisense drug development partners and the clinical successes of our antisense drugs, including mipomersen, we entered into a lease agreement in 2010 to lease 25,792 square feet of laboratory and office space adjacent to our manufacturing facility. We are in the process of renovating the facility and preparing it for its intended use. When we occupy the facility, we will use it for laboratory and office space and to provide additional storage for our manufacturing materials. Lease payments commence in June 2011 and the lease has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods.

Annual future minimum payments under operating leases as of December 31, 2010 are as follows (in thousands):

		Operating Leases
2011	$	3,507
2012		1,407
2013		1,424
2014		1,390
2015		1,333
Thereafter		23,339
Total minimum payments	$	32,400

Rent expense for the years ended December 31, 2010, 2009 and 2008 was $4.3 million, $4.6 million and $3.8 million, respectively. In connection with certain of our leases, we recognize rent expense on a straight line basis over the lease term resulting in a deferred rent balance of $793,000 and $572,000 at December 31, 2010 and 2009, respectively.

6. Stockholders’ Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2010 and 2009, there were no shares of Isis' Series A Convertible Exchangeable five percent Preferred Stock or Series B Convertible Exchangeable five percent Preferred Stock outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

In December 2010, our Preferred Share Purchase Rights Plan expired.

Common Stock

At December 31, 2010 and 2009, we had 200,000,000 shares of common stock authorized, of which 99,393,780 and 98,850,934 were issued and outstanding, respectively. As of December 31, 2010, total common shares reserved for future issuance were approximately 21,038,486.

We issued 475,000 and 1.7 million shares of common stock for stock option exercises and the Employee Stock Purchase Plan ("ESPP") purchases for the years ending December 31, 2010 and 2009, respectively. We received net proceeds from these transactions of $4.4 million and $13.2 million in 2010 and 2009, respectively.

Stock Option Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options 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, 2010, a total of 6,357,248 opti ons were outstanding, of which options to purchase 3,836,932 shares were exercisable, and 4,870,549 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which, as amended, provided for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. At December 31, 2010, a total of 2,757,255 options were outstanding, of which 1,892,736 shares were exercisable, and no shares were available for future grant under the 2000 Plan. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

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

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

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

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"). The 2002 Plan provides for the issuance of stock options to our non-employee directors for the purchase of 1,000,000 shares of our common stock. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2010, a total of 696,000 options were outstanding, 474,750 of the shares issued were exercisable and 191,000 shares were available for future grant u nder the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the 2000 ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 2.0 million shares authorized in the plan as of December 31, 2010. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase beginning with the offering ending in January 1, 2010.

During 2010, employees purchased and we issued to employees 109,463 shares under the ESPP at prices ranging from $7.84 to $9.44 per share. At December 31, 2010, 139,306 shares were available for purchase under the ESPP.

Stock Option Activity and Stock-Based Compensation Expense

The following table summarizes Isis' stock option activity for the year ended December 31, 2010 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2009	8,633	$ 11.56		
Granted	1,868	$ 10.86		
Exercised	(420)	$ 7.84		
Cancelled/forfeited/expired	(270)	$ 13.24		
Outstanding at December 31, 2010	9,811	$ 11.54	4.07	$ 9,890
Exercisable at December 31, 2010	6,204	$ 10.87	3.18	$ 9,540

The weighted-average estimated fair values of options granted were $5.53, $7.27 and $7.44 for the years ended December 31, 2010, 2009 and 2008, respectively. The total intrinsic value of options exercised during the years ended December 31, 2010, 2009 and 2008 were $905,000, $9.2 million and $11.2 million, respectively, which we determined as of the date of exercise. The amounts of cash received from the exercise of stock options were $3.3 million, $11.9 million and $11.1 million for the years ended December 31, 2010, 2009 and 2008, respectively. For the year ended December 31, 2010, the weighted-average fair value of options exercised was $10.00. As of December 31, 2010, total unrecognized compensation cost related to non-vested stock-based compensation plans was $9.1 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfe itures. We expect to recognize this cost over a weighted average period of 1.2 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 ESPP for the year ended December 31, 2010, 2009 and 2008 (in thousands, except per share data), which was allocated as follows:

	Year Ended December 31,		
	2010	2009	2008
Research and development	$ 10,148	$ 10,977	$ 10,578
General and administrative	2,011	2,408	2,708
Non-cash compensation expense related to stock options included in continuing operations	12,159	13,385	13,286
Non-cash compensation (benefit) expense related to stock options included in discontinued operations	—	(1,558)	1,777
Total	$ 12,159	$ 11,827	$ 15,063

Determining Fair Value

Valuation. We utilize the Black-Scholes model as our method of valuing 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, 2010, 2009 and 2008:

Employee Stock Options:

	December 31,		
	2010	2009	2008
Risk-free interest rate	2.7%	1.9%	3.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	55.5%	56.8%	55.2%
Expected life	5.1 years	4.9 years	4.6 years

Board of Director Stock Options:

	December 31,		
	2010	2009	208
Risk-free interest rate	2.7%	3.4%	3.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	57.7%	61.5%	65.2%

Expected life	7.8 years	7.7 years	7.6 years

ESPP:

	December 31,		
	2010	2009	2008
Risk-free interest rate	0.2%	0.3%	2.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	47.8%	56 .5%	61.4%
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options 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. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

Warrants

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. These warrants expire on April 7, 2011 and can be settled with unregistered shares of our common stock. As of December 31, 2010, 116,867 shares of common stock under the warrants remained outstanding.

7. Income Taxes

We have net deferred tax assets relating primarily to net operating loss carryforwards, or NOL's, and research and development tax credit carryfowards. Subject to certain limitations, we may use these deferred tax assets to offset taxable income in future periods. Since we have a history of losses and the likelihood of future profitability is not assured, we have provided a full valuation allowance for the deferred tax assets in our balance sheet as of December 31, 2010. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to increase their recorded value and a corresponding adjustment to increase income or additional paid in capital, as appropriate, in that same period.

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 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 fullest 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 usin g all of our allowable losses and tax credits to reduce our tax liability, our 2009 tax expense was $20.0 million.

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

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, 2002, 2006 and 2007 are currently being audited by California's Franchise Tax Board. We do not expect that the results of this examination will have a material effect on our financial condition or results of operations.

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

	Year Ended December 31,	
	2010	2009
Current:		
Federal	$ (73)	$ 2,919
State	165	4,879
	92	7,798
Deferred:		
Federal	—	(1,025)

State	—	(3,582)
Foreign	—	—
	—	(4,607)
Income Tax Expense	$ 92	$ 3,191

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

	Year Ended December 31,					
	2010		2009		2008	
Pre tax income	$ (61,251)		$ (31,765)		$ (14,519)	
Statutory rate	(21,438)	35.0%	(11,118)	35.0%	(5,082)	35.0%
State income tax net of federal benefit	(3,518)	5.7%	(1,825)	5.7%	(834)	5.7%
Net change in federal valuation allowance	26,869	(43.9)%	12,275	(38.6)%	23,182	(159.6)%
Tax credits	(3,175)	5.2%	3,401	(10.7)%	(7,389)	50.9%
Expired NOL's	—	—%	(879)	2.8%	(11,514)	79.3%
Noncontrolling interest	908	(1.5)%	3,562	(11.2)%	1,918	(13.2)%
Other	446	(.7)%	(2,225)	7.0%	(281)	1.9%
Effective rate	$ 92	(0.2)%	$ 3,191	(10.0)%	—	—

Significant components of our deferred tax assets and liabilities as of December 31, 2010 and 2009 are as follows (in thousands):

	Year Ended December 31,	
	2010	2009
Deferred tax assets:		
Net operating loss carryovers	$ 148,688	$ 82,378
R&D Credits	38,989	33,130
Capitalized R&D	26,932	30,879
Deferred Revenue	38,409	70,882
Accrued Restructuring	10,888	10,887
Other	19,396	21,696
Total deferred tax assets	$ 283,302	$ 249,852
Deferred Tax Liabilities:		
Convertible Debt	$ (12,275)	$ (15,559)
Intangible and Capital Assets	(5,156)	(5,879)
Net Deferred Tax Asset	$ 265,871	$ 228,414
Valuation Allowance	(265,871)	(228,414)
Net Deferreds	$ —	$ —

The deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2010 and 2009 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 $10.3 million 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, 2010, we have federal, California and foreign tax net operating loss carryforwards of approximately $402.0 million, $315.1 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 have federal and California research and development tax credit carryforwards of approximately $36.9 million and $12.9 million, respectively and federal Orphan Drug credits of $1.3 million. 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 t ax purposes and the shorter carryforward periods related to the state 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.

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.

The following table summarizes the gross amounts of unrecognized tax benefits without regard to reduction in tax liabilities or additions to deferred tax assets and liabilities if such unrecognized tax benefits were settled.

Reconciliation of unrecognized tax benefits (in thousands):	
Unrecognized tax benefits balance at January 1, 2010	$ 0
Increase (decrease) for prior period tax positions	8,231
Increase (decrease) for current period tax positions	737

Unrecognized tax benefits balance at December 31, 2010	$ 8,968

The balance of unrecognized tax benefits at December 31, 2010 of $9.0 million are tax benefits that, if recognized, would not impact our effective tax rates as long as they remain subject to a full valuation allowance. The net effect on the deferred tax assets and corresponding decrease in the valuation allowance at December 31, 2010 resulting from unrecognized tax benefits is $7.6 million. We have not recognized any accrued interest and penalties related to unrecognized tax benefits during the year ended December 31, 2010 due to our NOL and research credit carryforwards. We do not foresee any material changes to unrecognized tax benefits within the next twelve months. We recognize interest and/or penalties related to income tax matters in income tax expense.

8. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

GlaxoSmithKline

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

We received $40 million from GSK, including a $35 million upfront payment, which we are amortizing over the five year period of our performance obligation based on the research plan included in the agreement, and a $5 million milestone payment. During 2010, we recognized revenue of $10.3 million from our relationship with GSK. Our balance sheet at December 31, 2010 included deferred revenue of $29.8 million, related to the upfront payment. We are also eligible to receive milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We are eligible to receive license fees and milestone payments, totaling up to nearly $1.5 billion, if all six programs are successfully developed for one or more indications and commer cialized through pre-agreed sales targets. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

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 $125 million in funding for the development costs of mipomersen, which we expect to meet in 2011. Thereafter, we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme has a first right of negotiation for ISIS-SOD1$_{Rx}$.

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 two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the fair value of our common stock. We are amortizing this $100 million 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 2010, 2009 and 2008, we recognized revenue of $66.9 million, $66.4 million and $48.2 million, respectively, primarily related to the upfront payments we received from Genzyme, which represented 62 percent, 55 percent and 45 percent, respectively, of our total revenue for those years. Our Consolidated Balance Sheet at December 31, 2010 and 2009 included deferred revenue of $94.1 million and $160.4 million.

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, our glucagon receptor and GCCR programs. The collaboration ended and we regained the rights to drugs from both of these programs. We intend to move forward a more potent inhibitor for our GCGR program, which we identified as part of our collaboration with OMJP. We also intend to move forward the GCCR program.

During 2009 and 2008, we recognized revenue of $18.4 million and $31.9 million, respectively, related to the $45 million upfront licensing fee, the $5 million milestone payment and the annual research and development funding under this collaboration, which represented 15 percent and 30 percent, respectively, of our total revenue for those years. During 2010, we did not recognize any revenue from our relationship with OMJP.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. 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. We finished amortizing the $15 million upfront fee into revenue when our period of performance under the original agreement ended in April 2010. Under the agreement, we will also

receive up to $170 million for the achievement of pre-specified development and regulatory milestones for the first drug to reach the milestone, as well as additional milestone payments associated with development of follow-on compounds. Bristol-Myers Squibb will also pay us roy alties on sales of products resulting from the collaboration.

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. In March 2010, we earned a $6 million milestone payment from the initiation of clinical studies. In 2010, Bristol-Myers Squibb stopped the Phase 1 study of BMS-PCSK9$_{Rx}$ and discontinued development of the drug. In July 2010, we and Bristol-Myers Squibb extended our collaboration and license agreement by two years and will work together to discover a more potent PCSK9 antisense drug to move into development.

During 2010, 2009 and 2008, we recognized revenue of $12.2 million, $9.1 million and $12.0 million, respectively, related to the upfront licensing fee, milestone payments and the research funding from Bristol-Myers Squibb, which represented 11 percent, 8 percent and 11 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2009 included deferred revenue of $1.9 million related to the upfront licensing fee.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin, and LY2275796, an antisense inhibitor of eIF-4E, or eukaryotic initiation factor-4E. Eli Lilly and Company is responsible for the preclinical and clinical development of LY2181308. As of December 31, 2010, 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 we are continuing to develop the drug. Eli Lilly and Company has the right to reacquire ISIS-EIF4E$_{Rx}$ on predefined terms prior to the initiation of Phase 3 development. However, if we publicly disclose the results from a Phase 2 clinical study of ISIS-EIF4E$_{Rx}$, and Eli Lilly and Company elects not to license ISIS-EIF4E$_{Rx}$ on the predefined terms, then we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2009 and 2008, we earned revenue from our relationship with Eli Lilly and Company totaling $75,000 and $156,000, respectively. During 2010, we did not recognize any revenue from our relationship with Eli Lilly and Company.

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. 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 IND for Achaogen's aminoglycoside drug, ACHN-490. In 2010, we received a $2 million milestone payment from Achaogen as a result of the initiation of a Phase 2 study of ACHN-490. At December 31, 2010 and 2009, we owned le ss than 10 percent of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug, we will receive milestone payments totaling up to $36.5 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 2010 and 2009, we recognized $2 million and $500,000, respectively, in revenue from our relationship with Achaogen, which does not include any revenue from the equity we received from Achaogen. During 2008, we did not recognize any revenue from our relationship with Achaogen.

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a biotechnology company that was focused 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. Altair evaluated AIR645 in patients with asthma in a Phase 2 study. In this study, treatment with AIR645 reduced its intended target and patients tolerated the drug well. However, reducing the target did not produce enough therapeutic benefit to warrant continued development and Altair discontinued the program. In December 2010, we and Altair terminated our collaboration and license agreement and we reacquired AIR645 as well as Altair's assets related to AIR645. Altair distributed cash to its preferred sha reholders in December 2010, and we received $408,000 from that distribution. Our ownership of Altair was less than 10 percent at December 31, 2010 and 2009. During 2010, 2009 and 2008, we recognized revenue of $17,000, $79,000 and $207,000, 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 ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange and in February 2008, ATL licensed ATL1102 to Teva Pharmaceutical Industries Ltd. When Teva decided to continue the development of ATL1102, we earned $1.4 million of sublicense revenue, which we included in revenue in 2008. In 2009, we earned $2 million from Teva for manufacturing ATL1102 drug product. In March 2010, Teva terminated the licensing agreement for ATL1102 and returned to ATL rights to ATL1102.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration. In December 2010, ATL completed a successful offering and raised approximately $2.4 million that it will use to advance ATL1103. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL. In October 2009 we agreed to manufacture ATL1103 drug product for ATL in return for 18.5 million shares of ATL's common stock. Additionally, ATL will pay royalties to us on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

At December 31, 2010 and 2009, we owned less than 10 percent of ATL's equity. During 2010, we recorded revenue of $35,000 related to this collaboration compared to $401,000 and $1.6 million for 2009 and 2008, respectively. Our balance sheets at December 31, 2010 and 2009 included deferred revenue of $210,000 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 specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In September 2010, we participated in Atlantic Pharmaceuticals' financing by agreeing to sell to Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. At December 31, 2010 we owned approximately 12 percent of Atlantic Pharmaceuticals' equity compared with appro ximately 13 percent at December 31, 2009. 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. In 2010, Atlantic Pharmaceuticals announced that in response to requests received from healthcare professionals, it was to supply alicaforsen under international Named Patient Supply regulations for patients with inflammatory bowel disease, or IBD. Atlantic Pharmaceuticals is currently pursuing opportunities to fund further development of alicaforsen.

During 2010, 2009 and 2008, 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 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, 2010 and 2009, we owned less than 10 percent of Excaliard's equity and we have no remaining performance obligations.

In 2010 and 2011, we participated in Excaliard's financings at nominal amounts to maintain our ownership percentage. In addition, assuming Excaliard successfully develops and commercializes its first drug, we will receive milestone payments totaling up to $10.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs that Excaliard develops. We may also receive a portion of the fees Excaliard receives if it licenses drugs from our collaboration. During 2010, 2009 and 2008, we recognized revenue of $3,000, $290,000 and $384,000, respectively, which does not include any revenue from the equity we received from Excaliard. Our balance sheets at December 31, 2009 included deferred revenue of $3,000 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 investigational new drug, or 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 Ph ase 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, iCo has 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 at a nominal amount to maintain our ownership percentage. As a result, our ownership in iCo was approximately 10 percent at December 31, 2009. In January 2010, 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 December 31, 2010 was approximately 12 percent. During 2010, 2009 and 2008 we recognized revenue of $7,000, $14,000 and $7,000, respectively, 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 December 2009, OncoGenex licensed OGX-011 to Teva for the treatment of multiple cancer indications, for which we received $10 million of the upfront payment OncoGenex received from Teva. We are also eligible to receive 30 percent of up to $370 million in milestone payments OncoGenex may receive from Teva in addition to up to seven 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, 2010, OncoGenex had not achieved any milestone events 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 $4.2 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of the drug. As of December 31, 2010, OncoGenex had not achieved any milestone events related to OGX-427 but in January 2011, we earned a $750,000 milestone payment related to OncoGenex's phase 2 trial in men with metastatic prostate cancer.

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 $11.4 million in revenue from our relationship with OncoGenex. During 2010 and 2008, we did not recognize any revenue from our relationship with OncoGenex. Our balance sheet at December 31, 2010 included deferred revenue of $750,000 related to our relationship with OncoGenex.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and is associated with a wide variety of conditions including infection, cancer and chronic inflammation. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In addition to license and option fees, we are eligible to receive development and commercial milestone payments and royalties on sales of drugs licensed to Xenon under the collaboration and a portion of sublicense revenue. If Xenon identifies a development candidate, Xenon may take an exclusive license for the development and worldwide commercialization for this development cand idate. During 2010, we did not recognize any revenue from our relationship with Xenon.

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 ribonucleic acid, or 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 nominal milestone payment from Archemix related to the advancement of their aptamer drug that incorporates our technology. We will receive a portion of any su blicensing fees Archemix generates as well as milestone payments and royalties on Archemix' drugs that use our technology. During 2010 we recognized $25,000 in revenue from Archemix compared to $100,000 in 2009. 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 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. In December 2010, we earned a $375,000 milestone payment from Alnylam for the initiation of a Phase 1 study in their transthyretin, or TTR, program. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam at the time of the agreement. During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million and a net gain on investments of $6.2 million. As of December 31, 2010, we no longer own any shares of Alnylam.

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, 2010, we did not have an RNAi-based drug in clinical development.

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. Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million plus $2.6 million of research and development funding in 2009 and 2010. In November 2010, Alnylam terminated the ssRNAi research program and we recognized $4.9 million of revenue from the upfront fee that we were amortizing into revenue over the research term. As a result, any licenses to ssRNAi products 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, terminated. We continue to advance the development of ssRNAi technolo gy and during the course of the collaboration, we made improvements in the activity of ssRNAi compounds, including increased efficacy and potency as well as enhanced distribution.

As of December 31, 2010, we had earned a total of $37.1 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics that Alnylam has granted to pharmaceutical partners.

During 2010, 2009 and 2008, we generated revenue from our relationship with Alnylam totaling $10.3 million, $5.0 million and $4.6 million, respectively, representing nine percent, four percent and four percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2009 included deferred revenue of $8.6 million related to our agreement with Alnylam.

AVI BioPharma, Inc., formerly Ercole Biotech, Inc.

In May 2003, we and Ercole entered an agreement in which each party cross-licensed its respective intellectual property related to alternative RNA splicing. As part of the agreement, we granted Ercole an additional license to 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 2010, 2009 and 2008, we did not recognize any revenue from our relationship with Ercole.

External Project Funding

CHDI Foundation, Inc.

In November 2007, we entered into an agreement with CHDI, which provided us 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 and 2008, we recognized revenue of $1.7 million and $2.7 million, respectively, from our relationship with CHDI. In 2010, we did not recognize any revenue from our relationship with CHDI.

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 provided funding to offset the costs of t he 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

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

Abbott Molecular Inc.

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

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2009 and 2010 we did not recognize any revenue from our relationship with AMI.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is 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 may 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. Prior to 2010, we had assigned our rights to receive royalties for Macugen to Drug Royalty Trust 3. During 2009 and 2008, because of our agreement with Drug Royalty Trust 3, we did not recognize any revenue from our relationship with Eyetech. In 2010, we recognized $567,000 of revenue related to royalties for Macugen under our license to Eyetech.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. During 2010, 2009 and 2008, we recognized revenue of $1.8 million, $1.3 million and $1.2 million, respectively, from our relationship with Roche Molecular Systems. Our balance sheets at December 31, 2010 and 2009 included deferred revenue of $150,000 and $200,000, respectively, related to our agreements with Roche Molecular Systems.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense their technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of ribonuclease H, or RNase H, patents. In 2010 we recognized $20,000 in revenue from our relationship with Idera, compared to $10,000 in 2009. During 2008 we did not recognize any revenue from our relationship with Idera.

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 our second-generation chemistry. We expect these patents will expire in February 2013. Under the license, we paid IDT $4.9 million in license fees in 2001 and we will pay royalties on sales of any drugs utilizing the technology we licensed from IDT until the patents expire.

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to ISIS-SMN_{Rx}. If we successfully develop and commercialize a drug incorporating the technology we licensed from the University of Massachusetts, we will pay milestone payments to the University of Massachusetts totaling up to $650,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the University of Massachusetts a portion of any sublicense revenue we receive from sublicensing its technology, and a royalty on sales of ISIS-SMN_{Rx} in the United States if our product incorporates the technology we licensed from the University of Massachusetts.

Verva Pharmaceuticals Ltd.

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

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMNRx. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $900,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive from sublicensing the Cold Spring Harbor Laboratory's technology, and a royalty on sales of ISIS-SMN_{Rx} if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

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. 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.

sanofi-aventis

In June 2010, Regulus entered into a global, strategic alliance with sanofi-aventis to discover, develop, and commercialize microRNA therapeutics. The alliance includes $640 million of potential future milestone payments in addition to a $25 million upfront fee, a $10 million equity investment in Regulus that sanofi-aventis made in October 2010 and annual research support for three years with the option to extend two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. sanofi-aventis also received an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth up to an additional $50 million to Regulus. We and Alnylam are each eligible to receive 7.5 percent of the upfront payment and all potential milestone payments, in addition to royalties on product sales. As a result, in July 2010 we received a payment of $1.9 million representing 7.5 percent of the $25 million upfront fee from Regulus.

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 IBD, and in February 2010, Regulus and GSK expanded this alliance to include microRNA therapeutics targeting miR-122 for the treatment of hepatitis C virus, or HCV, infection. 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, including miR-122 for HCV. 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 $28 million in upfront payments from GSK, including $18 million in option fees and two $5 million notes. The notes 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 notes, and if the notes do not convert or if Regulus does not repay the notes by February 2013, we, Alnylam and Regulus may elect to repay the notes 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 pharmacolo gical 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 2010, 2009 and 2008, Regulus recognized revenue of $3.1 million, $3.0 million and $1.9 million, respectively, related to Regulus' collaboration with GSK.

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.

9. Segment Information and Concentration of Business Risk

Segment Information

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 alliances with GSK and sanofi-aventis.

The following is information for revenue, loss from operations and total assets by segment for the years ended December 31, 2010, 2009 and 2008 (in thousands).

Year ended December 31, 2010	Drug Discovery and Development	Regulus
Revenue:		
Research and development	$ 102,921	$ 8,601
Licensing and royalty	5,552	—
Total segment revenue	$ 108,473	$ 8,601
Loss from operations	$ (48,356)	$ (15,498)
Total assets as of December 31, 2010	$ 550,477	$ 59,703

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)

As a result of adopting the new accounting standard related to our investment in Regulus, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Therefore in 2010 we began presenting our net share of Regulus' operating results on a separate line in our Consolidated Statement of Operations called "Equity in net loss of Regulus Therapeutics Inc."

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:

	2010	2009	2008
Partner A	62%	55%	45%
Partner B	11%	8%	11%

Partner C	0%	15%	30%

Contract receivables from two significant partners comprised approximately 30 percent and 15 percent of our contract receivables at December 31, 2010. Contract receivables from one significant partner comprised approximately 92 percent of our contract receivables at December 31, 2009. Included in our contract receivables at December 31, 2010 was $544,000, representing 44 percent of our contract receivables, due from Regulus.

10. 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 2010 for employees under 50 years old and over 50 years old, respectively). We made approximately $449,000, $450,000 and $467,000 in matching contributions for the years ended December 31, 2010, 2009 and 2008, respectively.

11. 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 Bru ker. Discovery remains in its early stage. As such, we had no basis on which to predict or record a loss related to this claim as of December 31, 2010. We will continue to represent and defend Ibis in this matter.

12. 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, 2010, and 2009 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2010 Quarters				
Revenue(1)	$ 29,926	$ 23,503	$ 28,624	$ 26,420
Operating expenses(1)	34,806	42,175	37,571	42,277
Loss from operations(1)	(4,880)	(18,672)	(8,947)	(15,857)
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,658)	$ (25,154)	$ (12,454)	$ (13,985)
Basic and diluted net loss attributable to Isis Pharmaceuticals, Inc. common stockholders(2)	$ (0.10)	$ (0.25)	$ (0.13)	$ (0.14)

	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)(3)	185,305	(3,587)	(12,718)	(18,328)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(3)	$ 186,218	$ (2,730)	$ (11,582)	$ (16,840)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders(2)(3)	$ 1.91	$ (0.03)	$ (0.12)	$ (0.17)

(1) As a result of adopting the new accounting standard related to our investment in Regulus in 2010, we have excluded Regulus' operating results from our revenue, operating expenses and loss from operations and presented our net share of Regulus' operating results on a separate line in our Consolidated Statements of Operations called "Equity in net loss of Regulus Therapeutics Inc.", compared to the line-by-line consolidation in 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. See Note 2,&nbs p;*Investment in Regulus Therapeutics Inc.*, for additional details.

(2) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for the year.

(3) As a result of the sale of Ibis to AMI, in the first quarter of 2009 we recorded a $202.5 million gain related to the sale of Ibis to AMI less $16.8 million of income tax expense.

SECOND AMENDMENT TO LOAN AGREEMENT

THIS SECOND AMENDMENT TO LOAN AGREEMENT (this "Second Amendment") is made and entered into as of November 15, 2010, 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 and a First Amendment to Loan Agreement dated as of September 30, 2009 (collectively, 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, 2009 and the unaudited financial statement of Borrower and each Guarantor and for the quarter ended June 30, 2010.

"Scheduled Commitment Termination Date" means July 27, 2011.

2. This Second 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 Second Amendment shall remain in full force and effect and are hereby ratified and confirmed by Lender and Borrower.

4. This Second 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 Second 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/ Jeffrey P. Lanigan

Name Jeffrey P. Lanigan

Title Assistant Vice President

Borrower: **ISIS PHARMACEUTICALS, INC.**,
a Delaware corporation

By /s/ B. Lynne Parshall

Name B. Lynne Parshall

Title Chief Operating Officer and Chief Financial Officer Isis Pharmaceuticals, Inc.

[EXECUTION PAGE OF SECOND AMENDMENT TO LOAN AGREEMENT]

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, 333-168674) of Isis Pharmaceuticals, Inc. and in the related Prospectus of our reports dated February 28, 2011, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December&nb sp;31, 2010.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2011

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: February 28, 2011

/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: February 28, 2011

/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, 2010, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: February 28, 2011

/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.