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, 2013

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

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

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

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

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

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

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

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The NASDAQ Global Select Market was $2,572,530,925 as of June 30, 2013.*

The number of shares of voting common stock outstanding as of February 21, 2014 was 117,270,225.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 25, 2014 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 10, 2014 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 82 to 87 incorporates several documents by reference as indicated therein.

* Excludes 18,552,106 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, 2013. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

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

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

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO® is a registered trademark of Genzyme Corporation

KYNAMRO Cornerstone℠ is a service mark of Genzyme Corporation

Macugen® is a registered trademark of Eyetech

Vyndaqel® is a registered trademark of Wyeth LLC, a wholly owned subsidiary of Pfizer, Inc.

Zytiga® is a registered trademark of the Johnson & Johnson Corporation

CORPORATE INFORMATION

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

PART I

Item 1. Business

Overview

We are the leading company in antisense drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including severe and rare, cardiovascular, neurologic and metabolic diseases and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs.

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Our flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the U.S. Food and Drug Administration, or FDA, approved the marketing application for KYNAMRO for patients with HoFH. Genzyme, a Sanofi Company, has also obtained marketing approval in other countries, including Mexico, Argentina and South Korea, and is pursuing marketing approval in multiple additional markets. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and is leveraging this expertise to reach patients with HoFH, who are in desperate need of new treatment options. Genzyme is concentrating marketing and sales efforts on lipid specialists, and physicians who refer HoFH patients to these specialists, to reach patients with HoFH in the United States and other countries.

We have created a mature and broad pipeline that goes well beyond KYNAMRO. We have a pipeline of 31 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We believe five drugs in our pipeline could be in registration for marketing approval or on the market by 2018. One of these drugs, ISIS-APOCIII$_{Rx}$, is a triglyceride-lowering drug we designed to treat patients with severely high triglyceride levels, including patients with a severe and rare genetic condition called familial chylomicronemia syndrome, or FCS. We have completed a broad Phase 2 program demonstrating that ISIS-APOCIII$_{Rx}$ significantly reduced triglyceride and apolipoprotein C-III, or apoC-III, levels in patients when evaluated as a single agent and in combination with fibrates. We plan to initiate a Phase 3 program in 2014 to support a potential 2016 regulatory filing for marketing approval for ISIS-APOCIII$_{Rx}$. In addition to ISIS-APOCIII$_{Rx}$, we have several drugs in late-stage development that we believe represent significant near-term commercial opportunities, such as ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$. We designed these drugs to treat patients with severe and rare diseases, such as

transthyretin amyloidosis, or TTR, and spinal muscular atrophy, or SMA, and who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. ISIS-TTR$_{Rx}$ is already in Phase 3 development, and we plan to initiate a Phase 3 program for ISIS-SMN$_{Rx}$ midyear in 2014. We believe that both of these drugs have the potential to reach the market in the next several years. We also have numerous drugs in our pipeline advancing in Phase 2 clinical development. Each of these drugs, including ISIS-GCCR$_{Rx}$, ISIS-GCGR$_{Rx}$, ISIS-FXI$_{Rx}$ and ISIS-PTP1B$_{Rx}$, could represent significant near and mid-term licensing opportunities with the potential for Phase 2 data within the next nine to 15 months.

To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at an optimal time to maximize the near- and long-term value for each drug. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GlaxoSmithKline, or GSK, and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of smaller companies that can exploit our drugs and technology. We call these smaller companies our satellite companies. We benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. We also maintain our broad ribonucleic acid, or RNA, technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnership strategy, which allow us to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated six new partnerships that involve antisense drugs for the treatment of neurological diseases or cancer, including four strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. We have received more than $230 million in upfront payments and have the potential to earn nearly $6 billion in future milestone payments and licensing fees from these partnerships. In addition, we have the potential to earn nearly $3 billion in future milestone payments and licensing fees from our other partnered programs. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements. Since 2007, our partnerships have generated an aggregate of more than $1.1 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding.

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As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated $410 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Below is a list of some of our key accomplishments for 2013 and early 2014.

Drug Development Highlights

- We and Genzyme were successful in bringing KYNAMRO to the market in the United States, Mexico, South Korea and Argentina for patients with homozygous FH. These patients are at high cardiovascular risk and may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
  - We received a $25 million milestone payment from Genzyme related to the marketing approval of KYNAMRO by the FDA.
  - Genzyme notes trends toward increases in qualified physicians, prescriptions and patients on drug, with optimism that these trends will continue in 2014. Genzyme is supporting the commercial success of KYNAMRO by:
    - Qualifying hundreds of treating physicians under the KYNAMRO Risk Evaluation Mitigation Strategy, or REMS, program to prescribe KYNAMRO.
    - Completing a Phase 1 KYNAMRO study in Japan to support ongoing discussions with Japan regulatory authorities regarding the next steps in development.
    - Expanding KYNAMRO commercial markets by obtaining marketing approval for KYNAMRO in the United States, Mexico, Argentina and South Korea and pursuing regulatory approvals in other countries. Genzyme has stated that it has the infrastructure in place to successfully bring KYNAMRO to patients in these new markets.
- We reported five sets of positive Phase 2 data demonstrating that ISIS-APOCIII$_{Rx}$ can effectively lower triglyceride levels in patients with high to extremely high triglyceride levels and can work as effectively as a single agent or in combination with fibrates. In addition, we reported that treated patients with type 2 diabetes experienced improvements in glucose control with trends toward enhanced insulin sensitivity.
  - We published data in the journal Circulation Research demonstrating that antisense inhibition of ApoC-III produced significant reductions of ApoC-III and triglycerides in humans and other animal species.
  - We received European Orphan Drug Designation for ISIS-APOCIII$_{Rx}$ for the treatment of patients with familial chylomicronemia syndrome.
- We reported positive clinical data in children and infants with SMA demonstrating that ISIS-SMN$_{Rx}$ is well tolerated with increases in muscle function scores observed in the type 2/3 children.
  - We presented interim results from both multiple-dose Phase 2 studies in infants and children with SMA demonstrating that ISIS-SMN$_{Rx}$ continues to be well tolerated at all doses. In the infant study, all four infants from the 6 mg cohort have been in the study for over six months and all have received three doses of ISIS-SMN$_{Rx}$, and one infant has received a fourth dose of ISIS-SMN$_{Rx}$. In the childhood onset

study, we reported dose- and time-dependent increases in muscle function scores in children treated with multiple-doses of ISIS-SMN$_{Rx}$. In children treated with 9 mg of ISIS-SMN$_{Rx}$, we reported an average increase in muscle function score of 3.7 points.
    - We reported results from an assay that measures SMN protein levels in the cerebral spinal fluid. We observed dose-dependent increases in SMN protein levels in children treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies.
    - Dr. Kathy Swoboda presented follow up data from a single-dose open-label Phase 1 study of ISIS-SMN$_{Rx}$ in children with SMA at the International Congress of the World Muscle Society. In this study, data suggest that children from the two highest doses continued to show increases in muscle function scores up to 14 months after a single injection of ISIS-SMN$_{Rx}$.
    - Dr. Claudia Chiriboga reported Phase 1 data on ISIS-SMN$_{Rx}$ at the American Academy of Neurology. In this open-label study conducted in a small population, ISIS-SMN$_{Rx}$ was well tolerated in children with SMA and increases in muscle function scores were observed in a number of these children.
- We received a positive opinion on European Orphan Drug Designation in the EU for ISIS-TTR$_{Rx}$ for the treatment of patients with TTR amyloidosis.
- We and our partners reported positive data from six drugs including multiple results from Phase 2 studies of ISIS-SMN$_{Rx}$ and ISIS-APOCIII$_{Rx}$, and we added five drugs to our pipeline.
- We and our partners initiated clinical studies on ten drugs.

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Corporate Highlights

- We formed a broad strategic alliance with Biogen Idec to discover and develop antisense drugs to treat neurological disorders, which combines Biogen Idec's expertise in neurology with our leadership in antisense technology.
    - We received a $100 million upfront payment from Biogen Idec.
    - We are eligible to receive substantial milestone payments, license fees and royalty payments for all treatments developed through this collaboration.
- We formed a new alliance with Roche to discover and develop antisense drugs to treat Huntington's disease.
    - We received a $30 million upfront payment and are eligible to receive up to $362 million in a license fee and milestone payments.
    - In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed plus up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized.
    - We are also eligible to receive tiered royalties on sales of drugs arising from the alliance.
- We received $6 million from AstraZeneca related to the continuation of the research collaboration between AstraZeneca and us to discover and develop novel antisense drugs to treat cancer.
- In 2014 to date, we have earned more than $16 million in payments from our partners as our and our partners' drugs in development continue to mature.
- We successfully completed a public offering of common stock raising $173.3 million in net proceeds. We are using the proceeds from this offering to support the Phase 3 development of ISIS-APOCIII$_{Rx}$, retain other drugs longer in development and advance the rest of our pipeline.
- We added Mr. Breaux Castleman and Joseph Loscalzo, M.D., Ph. D. to our Board of Directors.
- Our founder, CEO and chairman of the board of directors, Stanley T. Crooke, Ph.D., M.D., was awarded the 2013 Director of the Year Award for Companies in Transition by the Corporate Directors Forum and the 2013 Distinguished Scientist Award by the San Diego section of the American Chemical Society.

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 antisense drugs interrupt the production of disease-causing proteins by targeting RNAs. RNAs are naturally occurring molecules in the body that provide the information the cell needs to produce proteins. When our antisense drugs bind to the specific RNAs of a particular gene, they will ultimately inhibit or alter the expression of the protein encoded in the target gene.

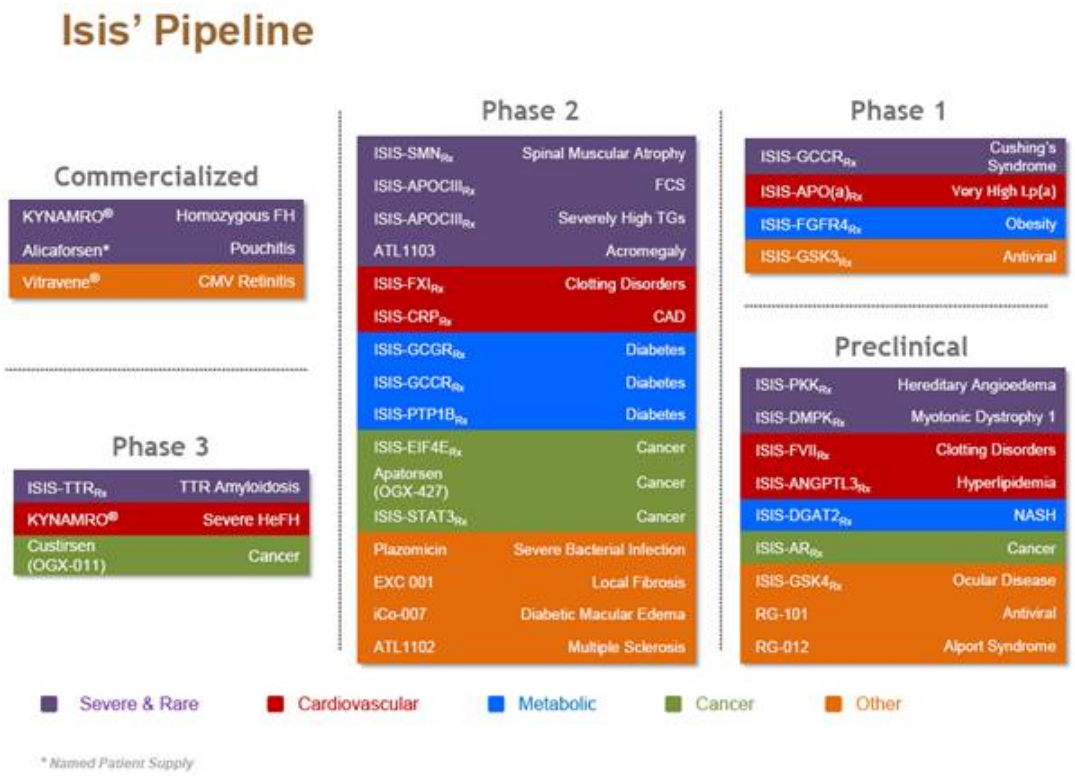
Our Development Projects

We are the leader in the discovery and development of an exciting class of RNA-targeted drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, 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, with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. We and our partners are developing antisense drugs for systemic, intrathecal and local delivery. We expect to continue to add new drugs to our pipeline, creating opportunities for future licensing transactions and building a broad proprietary portfolio of drugs applicable to many disease targets. We also continue to improve our scientific understanding of our drugs, including how our drugs impact the biological processes of the diseases we target.

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

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

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



KYNAMRO (mipomersen sodium) injection

Our flagship product, KYNAMRO, is on the market in the United States for patients with HoFH. These are patients who are at high cardiovascular risk and who are not able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies. KYNAMRO was approved by the FDA in January 2013 as an adjunct to lipid-lowering therapy and diet to reduce LDL-C, apolipoprotein-B, or apo-B, total cholesterol and non-high-density lipoprotein-cholesterol, or non-HDL-C, in patients with HoFH. KYNAMRO is available in the United States under a REMS with a Boxed Warning citing the risk of hepatic toxicity.

Genzyme is executing a comprehensive plan to address a global commercial market that consists of patients who are in desperate need of new treatment options for HoFH. Already Genzyme has obtained marketing approval for KYNAMRO in the United States, South Korea, Argentina and Mexico for use in patients with HoFH and is continuing to pursue approval in multiple additional markets. We believe that Genzyme has the commercial infrastructure and ability to successfully commercialize KYNAMRO worldwide making the drug available for patients in need in approved markets. In order to reach patients with HoFH in the United States Genzyme is concentrating marketing and sales efforts on lipid specialists, cardiologists, and physicians who treat these types of

patients. In the United States, Genzyme has established the KYNAMRO Cornerstone, a program offering services related to HoFH and KYNAMRO, including dedicated case management, reimbursement support, financial assistance for those who qualify, in-person injection training, and disease and product education for healthcare providers, patients, families, and caregivers. Genzyme also continues to raise awareness of HoFH. These activities include supporting continued medical educational programs to inform physicians about HoFH and partnering with key advocacy groups, such as Familial Hypercholesterolemia Foundation, the National Lipid Association, American College of Cardiology, International Symposium on Atherosclerosis and the American Heart Association.

KYNAMRO is a novel, first-in-class, apo-B synthesis inhibitor for the reduction of LDL-C. It is a second-generation antisense drug we discovered and licensed to Genzyme in 2008. KYNAMRO acts by decreasing the production of apo-B. Apo-B provides the structural core for atherogenic lipids, including LDL-C, which carry cholesterol through the bloodstream. KYNAMRO reduces LDL-C and other key atherogenic lipids linked to cardiovascular disease by preventing their formation. Together with Genzyme, we completed the largest randomized, double-blind, placebo-controlled trial conducted to date in HoFH patients. In this multi-center trial, KYNAMRO significantly further reduced LDL-C and all other measured endpoints when added to a treated baseline. In this trial, four patients (11 percent) treated with KYNAMRO withdrew due to adverse events. Consistent with other studies evaluating KYNAMRO, commonly observed adverse events included mild to moderate injection site reactions and flu-like symptoms, as well as elevations in liver transaminases.

Familial Hypercholesterolemia

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

HoFH is a severe form of FH. People with HoFH have inherited mutations that limit the body's ability to clear cholesterol. HoFH is extremely rare: it is believed to occur in only one out of every one million persons. As with other rare diseases, the true prevalence of HoFH may be underestimated because of inadequate data and under-diagnosis. Today, it is estimated that HoFH affects about 6,000 people globally. Medical literature includes different criteria for making the diagnosis of HoFH. There are multiple diagnostic criteria, which may include:

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

In addition to lipid-lowering medications, current standard-of-care for HoFH patients can include apheresis, a two to four hour process administered two to four times a month. Apheresis mechanically removes LDL-C from the blood and until recently it has been the primary therapy available on top of maximally tolerated lipid-lowering therapy.

Clinical Development

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

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

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

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

In 2012, Genzyme initiated a Phase 3 study titled 'evaluating the saFety and atherOgeniC lipoprotein redUction of mipomerSen in FH, or FOCUS FH. In FOCUS FH, Genzyme is evaluating KYNAMRO in patients with severe heterozygous FH. Severe HeFH patients are defined as FH patients who have LDL-C levels greater than 200 mg/dL with coronary artery disease or more than 300 mg/dL without coronary artery disease despite maintaining a regimen of maximally tolerated lipid-lowering therapy. In this 60-week, placebo-controlled, randomized, double-blind study, KYNAMRO is being administered either weekly as a 200 mg injection or three times a week as a 70 mg injection.

Severe & Rare Disease Franchise

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

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

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

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

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

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

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

We designed ISIS-TTR$_{Rx}$ to inhibit the production of all forms of TTR, and to offer an alternative approach to treat all types of TTR-related amyloidosis. ISIS-TTR$_{Rx}$ is the first drug to enter development under our preferred partner alliance with GSK. We have earned $24 million from GSK as ISIS-TTR$_{Rx}$ has advanced in development and are eligible to earn an additional $46 million in pre-licensing milestone payments to support the Phase 3 study of ISIS-TTR$_{Rx}$. In addition, we are eligible to earn regulatory and sales milestone payments from GSK should ISIS-TTR$_{Rx}$ achieve registration and meet certain sales thresholds. We are also eligible to receive double-digit royalties on sales of ISIS-TTR$_{Rx}$.

We completed a Phase 1 study evaluating the safety and activity of ISIS-TTR$_{Rx}$ in healthy volunteers. In this study, ISIS-TTR$_{Rx}$ produced rapid, dose-dependent reductions in plasma TTR protein with an average of 75 percent reduction in TTR protein, with some subjects achieving approximately 90 percent reduction. In addition, there were several subjects that reached TTR protein levels that were below the limit of assay detection. Subjects treated with ISIS-TTR$_{Rx}$ generally tolerated the drug well. In February 2013, we initiated a Phase 3 study to evaluate the efficacy of ISIS-TTR$_{Rx}$ in patients with FAP. In this study, we plan to enroll approximately 200 patients and evaluate the efficacy of ISIS-TTR$_{Rx}$ by measuring neurological dysfunction and quality of life in patients with FAP.

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

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

We designed ISIS-SMN$_{Rx}$ to potentially treat all types of childhood SMA by altering the splicing of a closely related gene, SMN2, which leads to the increased production of fully functional SMN protein. We developed a biomarker assay to measure levels of SMN protein in the cerebral spinal fluid of children and infants with SMA. In February 2014, we reported the first set of data using this biomarker assay. Using this assay, we observed dose-dependent increases in SMN protein levels in children with SMA treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies. In the single-dose study, SMN protein levels more than doubled in the two highest dose cohorts, 6 and 9 mg, with average increases of approximately 120 percent and 160 percent compared to baseline, respectively, approximately nine to 14 months after dosing. Similarly, in the multiple-dose study, we observed substantial increases in SMN protein levels in the 9 mg cohort of 115 percent compared to baseline approximately three months, or day 86, after the first dose.

In March 2013, we reported encouraging data from a single-dose, open-label Phase 1 clinical study evaluating ISIS-SMN$_{Rx}$ in children with SMA. In this study, we reported that ISIS-SMN$_{Rx}$ was well tolerated when administered intrathecally as a single dose directly into the spinal fluid. In addition, the children tolerated the intrathecal injection procedure well. We also showed that concentrations of ISIS-SMN$_{Rx}$ measured in cerebral spinal fluid were consistent with levels predicted from preclinical studies, indicating that the drug half-life in nervous system tissues is very long and that dosing once every six to nine months is feasible. Although the study was not designed to provide evidence of functional activity, we observed increases in the Hammersmith Functional Motor Scale-Expanded, or HFMSE, a measure of muscle function, in a number of these children. The mean increase in the HFMSE scores observed in the highest dose cohort (9 mg) at 3 months was 3.1 points or a 17.6% increase from baseline, with six of ten patients experiencing an increase of greater than four points. Observed increases in HFMSE scores equal to or greater than a 4 point compared to baseline were distributed by age with half in children under the age of five and half in children five and older.

In September 2013, we reported a follow-up analysis of the single-dose, open-label Phase 1 study of ISIS-SMN$_{Rx}$ in children with SMA. In this study, we observed that most children with SMA who received a single dose of one of the two highest doses of ISIS-SMN$_{Rx}$, 6 mg or 9 mg, continued to show increases in muscle function scores up to 14 months after a single injection of the drug.

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We are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA. In this study, we are evaluating four dose levels, 3, 6, 9, and 12 mg in children with SMA ages two to 15. We reported interim results from the 3, 6 and 9 mg cohorts from this study in February 2014 showing that treatment with ISIS-SMN$_{Rx}$ was well tolerated. In addition, we observed dose- and time-dependent increases in HFMSE scores in children treated with multiple doses of ISIS-SMN$_{Rx}$. Children in the 3 mg, 6 mg, and 9 mg cohorts achieved mean increases in HFMSE scores of 1.5, 2.3 and 3.7 points, respectively, nine months following the first dose of ISIS-SMN$_{Rx}$. Children in the 9 mg cohort achieved mean increases in HFMSE scores of 2.7 and 3.7 points three and nine months after the first dose of ISIS-SMN$_{Rx}$, respectively.

We are also evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants who have been diagnosed with SMA. In this study, we are evaluating two dose levels, 6 and 12 mg in infants with SMA. We reported interim results from this study in February 2014 showing that all four infants in the 6 mg cohort had been on study for over six months and are now approximately nine and a half to 16 months in age with an average age of approximately 12 and a half month. We reported that all four infants were alive and none had required permanent respiratory assistance. In addition, all four infants had tolerated intrathecal administration of ISIS-SMN$_{Rx}$ well. We plan to report more detailed results this study at the American Academy of Neurology meeting in April 2014.

We plan to initiate Phase 3 studies in both infants and children with SMA in 2014. We are designing these studies to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe.

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

ISIS-APOCIII$_{Rx}$ — ISIS-APOCIII$_{Rx}$ is an antisense drug we designed to reduce apoC-III protein production and lower triglycerides. ApoC-III regulates triglyceride metabolism in the blood and is an independent cardiovascular risk factor. This approach is validated by the fact that people who have certain mutations in the gene for apoC-III that result in lower levels of apoC-III have lower levels of triglycerides and lower instances of cardiovascular disease. Also, people with elevated levels of apoC-III have increased dyslipidemia associated with multiple metabolic abnormalities, such as insulin resistance and/or metabolic syndrome. In addition, people with elevated triglycerides are at increased risk for type 2 diabetes, and people with severely elevated triglycerides are at high risk for acute pancreatitis and other serious conditions.

We are developing ISIS-APOCIII$_{Rx}$ for patients with FCS and patients with severely high triglycerides. FCS is a rare orphan disease that affects an estimated 3,000 to 5,000 people worldwide. FCS patients often have triglyceride levels higher than 2,000 mg/dL and experience a number of health problems such as recurrent acute pancreatitis that often requires hospitalization, abdominal pain, and enlargement of the liver and spleen. We believe that the significant unmet medical need for an effective triglyceride-lowering drug for patients with FCS and the robust, consistent effects we observed with ISIS-APOCIII$_{Rx}$ should enable us to rapidly move this program forward toward the market.

We are also developing ISIS-APOCIII$_{Rx}$ for the treatment of patients with severely high triglycerides. These are patients with triglyceride levels greater than 880 mg/dL who are also at a higher risk of pancreatitis and other serious conditions. For all patients who cannot reduce their triglycerides to acceptable levels, the primary therapy is diet, which requires strict adherence and is often unsuccessful.

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

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

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Table 1: Comparison of the effects on key lipids for patients treated with 300 mg/week of ISIS-APOCIII$_{Rx}$

	Single Agent in Diabetics with High TG	Single Agent in Very High TG	In Addition to Fibrates in Very High TG	Single Agent in FCS
Baseline Mean mg/dL (range)				
ApoC-III	14 (9-20)	23 (14-33)	18 (12-30)	25 (19-35)
Triglycerides	259 (187-356)	559 (291-952)	394 (224-932)	1844 (1406-2083)
HDL-C	43 (35-55)	34 (22-52)	34 (14-53)	13 (8-16)
Non-HDL-C	178 (128-300)	175 (76-312)	185 (118-243)	262 (214-327)
Mean % Change from Baseline (Standard Deviation)				
ApoC-III	-88% (6.0)	-80% (9.3)	-70% (12.5)	-81% (9.8)
Triglycerides	-72% (8.3)	-71% (14.1)	-64% (8.9)	-69% (15.6)
HDL-C	+40% (19.8)	+46% (24.0)	+52% (23.7)	+78% (74.6)
Non-HDL-C	-28% (16.4)	-11% (38.3)	-19% (28.8)	-58% (14.3)

Consistent across the Phase 2 program, ISIS-APOCIII$_{Rx}$ demonstrated a good safety profile and was well tolerated. The most common adverse event was injection site reactions, which were predominantly mild and typically resolved rapidly. There were no flu-like symptoms, no treatment-related elevations in liver enzymes greater than three times the upper limit of normal, no abnormalities in renal function and no clinically meaningful changes in other laboratory values.

In 2014, we plan to initiate a Phase 3 program that will include evaluating ISIS-APOCIII$_{Rx}$ in patients with FCS and in patients with severely high triglyceride levels of greater than 880 mg/dL.

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

Antisense Therapeutics Limited, or ATL, is developing ATL1103 and has completed a Phase 1 study in healthy volunteers demonstrating that ATL1103 was safe and well tolerated. ATL is evaluating ATL1103 in a Phase 2 study in patients with acromegaly. ATL reported interim results from this study showing that patients treated with the highest dose, 200 mg twice weekly for 3 months, experienced an average of 30 percent reduction in serum insulin-like growth factor-I, or sIGF-I, the primary activity endpoint for the study. ATL plans to report the complete analysis from this study in 2014.

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

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We are currently evaluating ISIS-GCCR$_{Rx}$ in a Phase 2 study in patients with type 2 diabetes and plan to initiate a clinical study to evaluate ISIS-GCCR$_{Rx}$ in patients with Cushing's Syndrome in 2014.

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

In 2014, we plan to initiate a Phase 1/2 clinical study evaluating ISIS-PKK$_{Rx}$ in healthy volunteers and in patients with hereditary angioedema. We plan to report data from this study in late 2014 or early 2015.

ISIS-DMPK$_{Rx}$ — ISIS-DMPK$_{Rx}$ is an antisense drug we designed to correct the underlying genetic defect that causes Myotonic Dystrophy Type 1, or DM1. DM1 is the most common form of muscular dystrophy in adults. It is caused by a genetic defect in the dystrophia myotonica-protein kinase, or DMPK, gene in which a sequence of three nucleotides, CTG, repeats extensively. This DNA expansion produces an abnormally large toxic RNA that

accumulates in cells, including muscle cells, and prevents production of proteins essential for normal cellular function. In addition to disabling muscle spasms and progressive muscle wasting and weakness, DM1 also affects many other organs within the body. Patients with DM1 can experience insulin insensitivity, cataracts and infertility. DM1 is estimated to affect approximately 150,000 patients in the United States, Europe and Japan. The severity and age of onset of DM1 correlates with the number of times the three nucleotides repeat, which increases from one generation to the next. Currently, there are no disease-modifying therapies for patients with DM1 and treatments are intended only to manage symptoms.

In 2012, we and Biogen Idec entered into an alliance that provides Biogen Idec an option to develop and commercialize ISIS-DMPK$_{Rx}$. Under the agreement, we received an upfront fee and are responsible for developing ISIS-DMPK$_{Rx}$. Biogen Idec has the option to license ISIS-DMPK$_{Rx}$ up through completion of the Phase 2 study. We will receive milestone payments from Biogen Idec as ISIS-DMPK$_{Rx}$ advances through development.

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

In 2014, we plan to initiate a Phase 1/2 clinical study evaluating ISIS-DMPK$_{Rx}$ in healthy volunteers and in patients with DM1.

Cardiovascular Franchise

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

Cardiovascular disease is an area of focus for us. We have created a cardiovascular disease franchise comprised of drugs that target all the key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis, an aberrant blood clot formation responsible for most heart attacks and strokes. For example, we are developing a drug that lowers apoC-III and triglycerides, which are both independent risk factors for cardiovascular disease. A recent addition to our cardiovascular franchise is our drug that lowers Lp(a), another independent risk factor for cardiovascular disease. Currently available lipid-lowering therapies do not significantly lower apoC-III, triglycerides, or Lp(a). We believe that targeting apoC-III and Lp(a) could provide a complementary approach to lipid-lowering therapies, including KYNAMRO.

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ISIS-APOCIII$_{Rx}$ — ISIS-APOCIII$_{Rx}$ is an antisense drug we designed to reduce apoC-III protein production and lower triglycerides. In 2014, we plan to initiate a Phase 3 program that will include evaluating ISIS-APOCIII$_{Rx}$ in patients with FCS and in patients with severely high triglyceride levels of greater than 880 mg/dL. For more information on ISIS-APOCIII$_{Rx}$, please refer to the ISIS-APOCIII$_{Rx}$ section under the subheading “Severe and Rare Disease Franchise”.

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

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

In 2012, we initiated a Phase 2 study evaluating ISIS-FXI$_{Rx}$ in patients undergoing knee replacement surgery, also referred to as total knee arthroplasty, or TKA. This study is a comparator-controlled study, in which we will compare the safety and activity of ISIS-FXI$_{Rx}$ to a commonly used anti-coagulant, enoxaparin. In this study, we are evaluating the effectiveness of ISIS-FXI$_{Rx}$ in reducing the number of thrombotic events in patients following TKA without increasing bleeding. Given the mechanism of Factor XI inhibition, we believe that doctors could use our drug broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic drugs are needed. We plan to report data on ISIS-FXI$_{Rx}$ from the Phase 2 study in patients undergoing TKA in 2014.

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

In preclinical studies, we observed that our antisense inhibitor of CRP suppressed liver and serum CRP levels. We evaluated ISIS-CRP$_{Rx}$ in a Phase 1 study in which ISIS-CRP$_{Rx}$ produced statistically significant reductions in CRP in the cohort of subjects that entered the study with elevated levels of CRP. We also evaluated ISIS-CRP$_{Rx}$ in healthy volunteers who were subjected to an endotoxin challenge, which caused an increase in CRP and other inflammatory markers. In this study, we showed that pretreatment with ISIS-CRP$_{Rx}$ was able to blunt the acute increase in CRP. In our Phase 2 program, we are evaluating ISIS-CRP$_{Rx}$ in different disease settings where elevated levels of CRP are associated with a worsening of disease symptoms. The first of these Phase 2 studies evaluated ISIS-CRP$_{Rx}$ in patients with rheumatoid arthritis, or RA, with chronically elevated CRP. In this study, patients treated with ISIS-CRP$_{Rx}$ achieved rapid, dose-dependent mean reductions of up to 67 percent in CRP. Patients also showed improvements in signs and symptoms of RA, which correlated with reductions in CRP, but were not sufficiently greater than improvements observed in the placebo group to justify further development of ISIS-CRP$_{Rx}$ for RA.

We are also evaluating ISIS-CRP$_{Rx}$ in a Phase 2 study in patients with atrial fibrillation, or AF. AF involves an irregular heart rate that commonly causes poor blood flow to the body. In this study, we are evaluating the effect of lowering CRP on the frequency and duration of AF. We plan to report data on ISIS-CRP$_{Rx}$ from the Phase 2 study in patients with AF in 2014.

ISIS-APO(a)$_{Rx}$ — ISIS-APO(a)$_{Rx}$ is an antisense drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing Lp(a), an independent risk factor for cardiovascular disease. Scientists associate high levels of Lp(a) with an increased risk of atherosclerosis, coronary heart disease, heart attack and stroke. Lp(a) levels in blood can vary greatly between individuals due primarily to genetic variations between individuals. Lp(a) levels are genetically determined, reached by the age of two and remain constant throughout the life of the individual. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies do not adequately reduce Lp(a) to acceptable levels in patients with elevated Lp(a). As a general guideline for ideal Lp(a) levels, the European Atherosclerosis Society recommends that Lp(a) be less than or equal to 50 mg/dL. Even patients who can control their LDL-C remain at high-risk of cardiovascular events if they have high levels of Lp(a). There is a significant need for a highly specific drug that can lower Lp(a).

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

We plan to initiate a Phase 2 program for ISIS-APO(a)$_{Rx}$ in patients with high risk of cardiovascular disease and high Lp(a) levels in 2014.

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

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

We plan to complete our preclinical evaluation of ISIS-FVII$_{Rx}$ in 2014.

ISIS-ANGPTL3$_{Rx}$ — ISIS-ANGPTL3$_{Rx}$ is an antisense drug we designed to reduce angiopoietin-like 3 protein, or ANGPTL3, an independent risk factor for cardiovascular disease. ANGPTL3 is produced in the liver and regulates lipid, glucose and energy metabolism. Humans with elevated levels of ANGPTL3 have hyperlipidemia that is associated with an increased risk of premature heart attacks, increased arterial wall thickness as well as multiple metabolic abnormalities, such as insulin resistance. In contrast, humans with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels and a lower risk of cardiovascular disease. In preclinical studies, antisense inhibition of ANGPTL3 resulted in robust reductions of multiple lipid parameters, including total-cholesterol, LDL-C and triglycerides.

We plan to initiate a Phase 1 study for ISIS-ANGPTL3$_{Rx}$ in 2014 with the potential to report data from this study in late 2014 or early 2015.

Metabolic Franchise

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

Metabolic disease is a very large area of medical need and is another area in which we focus our drug discovery efforts. Our approach is to develop antisense drugs that doctors can add to existing therapies to treat diabetes. One hurdle for traditional drug development is that most traditional drugs cannot selectively target a disease-causing protein without also affecting closely related proteins, which often results in unwanted side effects. We design our antisense drugs to target the gene responsible for producing the disease-causing protein while avoiding unwanted effects on closely related proteins, thereby reducing the risk of side effects.

We now have three drugs in Phase 2 studies in our pipeline to treat type 2 diabetes, each of which acts upon targets in the liver or fat tissue through a distinct mechanism to improve insulin sensitivity, reduce glucose production, or affect other metabolic aspects of this complex disease.

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

We are developing ISIS-GCGR$_{Rx}$ to help provide better glucose control for patients with type 2 diabetes. In preclinical studies using the most insulin-resistant models of type 2 diabetes, antisense reduction of GCGR decreased excessive liver glucagon action, produced robust glucose control, reduced levels of triglycerides and helped preserve the pancreas without producing hypoglycemia. Although researchers have developed and evaluated small molecule inhibitors of GCGR and observed glucose-lowering effects, treatment with these small molecule inhibitors also produced side effects, including increases in lipids and blood pressure, limiting their potential use as drugs.

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We have completed a Phase 1 study evaluating the safety of ISIS-GCGR$_{Rx}$ in healthy volunteers. In this study, subjects tolerated ISIS-GCGR$_{Rx}$ well with no clinically significant increases in lipids or blood pressure and with no hypoglycemic events. In addition, we observed an increase in total GLP-1, which was consistent with our preclinical observations.

Given the unique mechanism of action and good tolerability observed in the Phase 1 study, we believe that doctors could use ISIS-GCGR$_{Rx}$ in diabetic patients with severe hyperglycemia who are not controlled with current treatments and who could benefit from a drug that significantly decreases glucose levels and preserves pancreatic function.

We are currently evaluating ISIS-GCGR$_{Rx}$ in a Phase 2 study in patients with type 2 diabetes who, despite taking metformin, have uncontrolled glucose levels.

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

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

We believe that doctors could use ISIS-GCCR$_{Rx}$ in diabetic patients with moderate to severe hyperglycemia who are also obese or have high levels of cholesterol and triglycerides. We also believe that there are other attractive therapeutic opportunities for doctors to use ISIS-GCCR$_{Rx}$ in patients with diseases in which there is glucocorticoid excess, such as Cushing's Syndrome, and other diseases where a selective GCCR inhibitor could be beneficial. We plan to develop ISIS-GCCR$_{Rx}$ to treat patients with Cushing's Syndrome. For more information on ISIS-GCCR$_{Rx}$ and Cushing's Syndrome, please refer to the ISIS-GCCR$_{Rx}$ section under the subheading "Severe and Rare Disease Franchise".

We are currently evaluating ISIS-GCCR$_{Rx}$ in a Phase 2 study in patients with type 2 diabetes in combination with metformin and plan to initiate a Phase 2 study evaluating ISIS-GCCR$_{Rx}$ in patients with Cushing's Syndrome in 2014.

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

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

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

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

We are currently evaluating ISIS-PTP1B$_{Rx}$ in a Phase 2 study in patients with type 2 diabetes who, despite taking metformin or metformin plus sulfonylurea, have uncontrolled glucose levels.

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

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

We plan to report data from the Phase 1 study in 2014.

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

We plan to complete preclinical evaluation of ISIS-DGAT2$_{Rx}$ in 2014.

Cancer Franchise

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

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

We believe the favorable tolerability and early evidence of clinical benefit of the anti-cancer drugs in our pipeline demonstrate how uniquely suited our technology is to create novel cancer therapeutics. In addition, we believe our generation 2.5 chemistry enhances the potency and effectiveness of our antisense drugs, and extends the applicability of our technology to cancers that are difficult to treat. For instance, we presented positive interim Phase 1 data on our first generation 2.5 drug, ISIS-STAT3$_{Rx}$, in patients with advanced cancer who did not adequately respond to prior chemotherapy treatment. In this interim analysis, we observed clear responses in these patients with an acceptable safety profile. Based on these data, we and AstraZeneca are currently evaluating ISIS-STAT3$_{Rx}$ in a clinical study in focused patient populations with advanced cancer.

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

Teva and OncoGenex are collaborating on a global Phase 3 clinical program in patients with metastatic castrate resistant prostate cancer, or CRPC, and metastatic non-small cell lung cancer, or NSCLC. OncoGenex and Teva are evaluating custirsen in two Phase 3 clinical studies for first- and second-line chemotherapy in patients with metastatic CRPC. OncoGenex and Teva are also evaluating custirsen in a Phase 3 study as a second-line treatment in patients with NSCLC. Teva and OncoGenex have completed enrollment for the SYNERGY study as a first-line treatment in patients with CRPC. OncoGenex has stated that the FDA has agreed on the design of the SYNERGY trial, a Phase 3 study evaluating custirsen, via the special protocol assessment, or SPA, process. A SPA is an agreement between the FDA and the drug developer that the design and planned analysis of a study is sufficient to address objectives in support of a regulatory submission. Teva and OncoGenex expect to report results for the survival primary endpoint from the SYNERGY study in 2014.

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

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

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

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

In 2010, we initiated a Phase 2 program of ISIS-EIF4E$_{Rx}$ in patients with NSCLC and prostate cancer. The endpoints for both studies include progression-free survival, overall survival, response rates, time to progression and the reduction of a variety of biomarkers. We plan to report data from the Phase 2 program in 2014.

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

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

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

OncoGenex has initiated a broad Phase 2 program evaluating apatorsen in six Phase 2 studies in patients with cancer. In September 2012, OncoGenex reported preliminary results from a Phase 2 study in patients with CRPC. In this study, OncoGenex reported that treatment with apatorsen in combination with prednisone resulted in a higher number of patients without disease progression at 12 weeks and greater declines in prostate-specific antigen, or PSA, and circulating tumor cells compared to patients treated with prednisone alone. OncoGenex is also evaluating apatorsen in a Phase 2 study, referred to as Pacific, in combination with Zytiga and prednisone in patients with metastatic CRPC who have PSA progression.

OncoGenex has reported the initiation of several investigator-sponsored studies for apatorsen. The Spruce study is a Phase 2 investigator-sponsored study designed to evaluate progression-free survival benefit of apatorsen in combination with carboplatin/pemetrexed therapy in patients with previously untreated Stage IV non-squamous NSCLC. The Rainier study is a Phase 2 investigator-sponsored study designed to evaluate overall survival benefit of apatorsen in combination with Abraxane and gemcitabine therapy in patients with previously untreated metastatic pancreatic cancer.

In a Phase 2 study, referred to as Borealis-1, OncoGenex is evaluating overall survival benefit of apatorsen in combination with gemcitabine and cisplatin in patients with metastatic bladder cancer. OncoGenex is also evaluating apatorsen in a Phase 2 study, Borealis-2, in combination with docetaxel in patients with advanced or metastatic bladder cancer. OncoGenex expects to report data from the Borealis-1 study in the second half of 2014.

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

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

ISIS-STAT3$_{Rx}$ is our first drug to incorporate our new generation 2.5 chemistry. We believe the significant potency we observed in our preclinical studies with ISIS-STAT3$_{Rx}$ broadens the therapeutic opportunities for ISIS-STAT3$_{Rx}$ into many different types of cancer where STAT3 is implicated. Our initial focus is to evaluate ISIS-STAT3$_{Rx}$ in hematologic malignancies, such as lymphoma. Together with AstraZeneca, we have designed a development plan that could allow for a rapid path to the market in these patient populations. AstraZeneca has already initiated a Phase 1/2 study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC, a type of liver cancer, and will be evaluating additional therapeutic opportunities.

In preclinical studies, ISIS-STAT3$_{Rx}$ demonstrated antitumor activity in animal models of human cancer with an attractive safety profile. In 2012, we reported interim Phase 1 data in patients with cancer who did not adequately respond to prior chemotherapy treatment. In this study, we showed that ISIS-STAT3$_{Rx}$ treatment resulted in clear responses in patients with advanced cancer with an acceptable safety profile. Based on these data, we initiated a Phase 2 study in focused patient populations with advanced cancer. We plan to report data from this Phase 2 study at a future scientific meeting.

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

ISIS-AR$_{Rx}$, also referred to as AZD5312 and previously referred to as ISIS-AZ1$_{Rx}$, is part of our collaboration with AstraZeneca to discover and develop anti-cancer drugs. As ISIS-AR$_{Rx}$ progresses in development, we are eligible to receive milestone payments as well as royalties on sales if ISIS-AR$_{Rx}$ is successfully commercialized. ISIS-AR$_{Rx}$ is the second drug in our cancer franchise to incorporate our new generation 2.5 chemistry.

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In preclinical studies, ISIS-AR$_{Rx}$ demonstrated antitumor activity in animal models of prostate cancer, including a model resistant to enzalutamide, a small molecule antagonist often used in patients with castration-resistant prostate cancer. AstraZeneca plans to initiate a Phase 1/2 study for ISIS-AR$_{Rx}$ in

patients with AR-related cancers in 2014.

Other Drugs in Development

The broad applicability of our antisense technology allows us to create promising drugs, such as the ocular and antiviral drugs under our preferred partner collaboration with GSK, in a variety of disease areas. We have successfully developed novel drugs designed to treat many different diseases. In therapeutic areas that are outside of our core areas of development, we have licensed our drugs to highly focused satellite companies that have the specific expertise and resources to continue developing the drugs. Together with our partners we continue to advance drugs in clinical development that are outside of our core therapeutic areas.

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

Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli, and against methicillin-resistant staphylococcus aureus, or MRSA. In preclinical studies, plazomicin demonstrated an acceptable safety profile and the potential for once-daily dosing. Achaogen has completed a Phase 1 study of plazomicin in healthy volunteers and a Phase 2 study. In the Phase 2 study, Achaogen evaluated plazomicin compared to levofloxacin for the treatment of complicated urinary tract infections and acute kidney infections in adults. In this study, patients treated with plazomicin tolerated the drug well and patients demonstrated favorable activity of plazomicin as compared to levofloxacin.

In 2014, Achaogen plans to initiate a Phase 3 study evaluating plazomicin in patients with serious multi-drug resistant, or MDR, gram-negative bacterial infections. Achaogen announced that it had reached agreement with the FDA to conduct the study under a SPA. Achaogen reported that the Phase 3 study is designed as a superiority study to evaluate the efficacy and safety of plazomicin compared with colistin in patients with bloodstream infections and nosocomial pneumonia caused by a class of MDR bacteria known as carbapenem-resistant enterobacteriaceae.

EXC 001 — EXC 001 is an antisense drug that targets connective tissue growth factor, or CTGF, a growth factor that is over-expressed in damaged skin or tissue following a traumatic event. We co-discovered EXC 001 with Excaliard Pharmaceuticals, Inc. and exclusively licensed it to Excaliard for the local treatment of fibrotic diseases, including scarring. Fibrosis represents a significant and expanding area of unmet medical need where antisense drugs could offer a unique advantage as anti-fibrotic agents. In November 2011, Pfizer Inc. acquired Excaliard. Pfizer continues to evaluate EXC 001 in a Phase 2 program designed to provide information, including the optimization of the dose, for the design of the Phase 3 program for EXC 001.

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

In May 2010, investigators evaluating iCo-007 in patients with diffuse diabetic macular edema presented positive results from the Phase 1 study showing that subjects tolerated iCo-007 well. In this study, a number of individuals exhibited a decrease of central macular edema compared to baseline using an analytical method called optical coherence tomography. iCo is currently evaluating iCo-007 in a Phase 2 study in patients with diabetic macular edema and plans to report data in 2014.

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

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

We are currently evaluating ISIS-GSK3$_{Rx}$ in a Phase 1/2 study in healthy volunteers and patients and expect to complete this study in 2014.

ISIS-GSK4$_{Rx}$ — ISIS-GSK4$_{Rx}$ is an antisense drug we designed to an undisclosed target to treat an ocular disease. We are developing ISIS-GSK4$_{Rx}$ as part of our collaboration with GSK. We are eligible to receive milestone payments from GSK as ISIS-GSK4$_{Rx}$ advances in development, and we are responsible for developing the drug up to Phase 2 proof-of-concept, at which time GSK has the option to pay us a license fee and license ISIS-GSK4$_{Rx}$ from us. We are also eligible to receive double-digit royalties on sales of ISIS-GSK4$_{Rx}$.

We plan to initiate preclinical studies to support an investigational new drug application for ISIS-GSK4$_{Rx}$ in 2014.

RG-101 — RG-101 is a preclinical drug that Regulus Therapeutics Inc., a company we co-founded focused on microRNA therapeutics, is developing. An oligonucleotide that inhibits microRNA, RG-101 is an anti-miR that targets microRNA-122, or miR-122. Researchers believe that miR-122 is essential for the replication of hepatitis C virus, or HCV, suggesting that an anti-miR-122 drug may reduce HCV infection and improve HCV-associated pathologies like fatty liver.

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

Regulus currently plans to develop RG-101 as a key component of an HCV combination regimen for patients who have failed, or are intolerant of, the current standard of care and for specific patient populations, such as patients with HCV/HIV co-infections. Regulus plans to initiate a Phase 1 study for

RG-101 in healthy volunteers in 2014.

RG-012 — RG-012 is a preclinical drug candidate Regulus is developing, which is an anti-miR that targets microRNA-21, or miR-21. Regulus reports that subcutaneous administration of RG-012 significantly decreased the rate of renal fibrosis and increased the lifespan of mice treated with RG-012 up to 50 percent in a mouse model of Alport Syndrome. Alport Syndrome is a life-threatening disease in which patients experience progressive loss of kidney function.

Regulus currently plans to develop RG-012 to proof-of-concept. At that stage of development, Regulus' partner Sanofi has an exclusive option to license. We are eligible to receive a portion of all milestone payments and royalties Regulus receives from Sanofi if Sanofi chooses to exercise its option to license RG-012 from Regulus and RG-012 advances in development.

Antisense Technology

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

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

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

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

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

We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drugs. The goal of our target-based research programs is to identify antisense drugs to treat diseases for which there are large commercial markets or for which there is a need for better drugs. In addition, our research programs focus on the planned advancement of our technology for future antisense drugs. We selected our next generation chemistry, generation 2.5, an advancement that we believe will increase the potency of our drugs and make oral administration commercially feasible. In 2013, we published data demonstrating that our generation 2.5 drugs generally have enhanced potency over our generation 2.0 drugs and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland and peripheral nerves. We expect that these generation 2.5 drugs will constitute some of our future drugs and serve as follow-on compounds to some of our current drugs in development. Currently our ISIS-$STAT3_{Rx}$, ISIS-$FVII_{Rx}$, and ISIS-AR_{Rx} drugs incorporate our generation 2.5 chemistry.

Other Antisense Targets and Mechanisms

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

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In addition, the diversity of our technology provides us with the potential to utilize many different antisense mechanisms, like alternative splicing. Because splicing occurs at the RNA level, we can utilize our technology to direct splicing to produce a particular protein product. For example, SMA is a splicing disorder caused by a loss of, or defect in, the survival motor neuron 1, or SMN1, gene leading to a decrease in the protein SMN. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. We designed our ISIS-SMN$_{Rx}$ drug to alter the splicing of a similar gene, SMN2, to increase production of a fully functional SMN protein. ISIS-SMN$_{Rx}$ is currently being evaluated in Phase 2 studies in infants and children with SMA. There are a number of diseases, including cystic fibrosis and Duchenne muscular dystrophy, which scientists believe are splicing disorders. These are diseases we could potentially treat using antisense modulation of splicing.

Because there are many different types of RNA that exist within the body, our antisense technology is not limited to RNA sequences that translate into proteins, but rather we can apply the principles of our technology to develop drugs that target other non-coding RNAs, such as toxic RNAs. For example, DM1 is a form of muscular dystrophy that is caused by an abnormally long, toxic RNA that accumulates in cells and prevents the production of proteins essential for normal cellular function. We designed our drug, ISIS-DMPK$_{Rx}$, to target and reduce the toxic DM1 RNA. In our preclinical studies, we observed effective reductions of the toxic RNA that led to a reversal of disease symptoms that was sustained for up to one year in a mouse model of disease.

Another interesting RNA target for our antisense technology is microRNAs. To date, scientists have identified more than 700 microRNAs in the human genome, and have shown that the absence or presence of specific microRNAs in various cells is associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam Pharmaceuticals, Inc. established Regulus as a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Regulus plans to advance a development candidate into clinical studies in 2014.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a development pipeline of 31 drugs, to create a broad base of potential license fees, milestone payments, royalties, profit sharing and earn out payments and to control our drug development expenses. In this way, we remain a focused and efficient research and development organization that can continue to discover new drugs and expand our and our partners' pipelines.

Through the efficiency of our drug discovery platform we can develop drugs to almost any gene target. We concentrate on developing antisense drugs in our core therapeutic areas with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. We believe our partnering strategy provides us the flexibility to maximize the near- and long-term value of our drugs by licensing each of our drugs at the right time with the right partner. Using this strategy, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. Just as we have advanced and matured our technology and pipeline, we have evolved our partnering strategy in order to maximize the value of each of our assets. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a broad base of license fees, milestone payments, profit share and royalty income. For example, we have a broad portfolio of drugs to treat type 2 diabetes. We are developing each of these drugs through Phase 2 development, and we plan to report proof-of-concept data on each of these drugs within the next 12 to 18 months. Because late-stage clinical development for type 2 diabetes can be large and expensive, we will seek a partner to license these drugs and conduct late-stage clinical development and commercialization. With the potentially competitive benefit of our drugs over existing therapies and clinical proof-of-concept data, we believe that we could license each of these drugs to a partner on lucrative economic terms.

We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. As in our other partnerships, we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

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And finally, we plan to keep some drugs longer so we can conduct Phase 3 development on our own without a partner. By doing so, we believe we can maximize the value of these drugs by licensing them much later in development and potentially maintaining a larger portion of the commercial revenue. Our novel triglyceride-lowering drug, ISIS-APOCIII$_{Rx}$, is an example of a drug that we plan to develop into and perhaps through Phase 3 development on our

own. We believe we have the resources to conduct a broad Phase 3 program on ISIS-APOCIII$_{Rx}$, and because of our experience in the cardiovascular space with KYNAMRO, we have the expertise to conduct the Phase 3 studies. We plan to initiate a Phase 3 program on ISIS-APOCIII$_{Rx}$ this year in patients with FCS and patients with severely high triglycerides of greater than 880 mg/dL.

We also work with a consortium of smaller companies that can exploit our drugs and technologies outside our primary areas of focus. We call these smaller companies our satellite companies. We benefit from the disease-specific expertise of our satellite company drug development partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. Through this strategy we can expand the therapeutic range of antisense drugs into diseases that need new and innovative treatment options. We provide more information on our satellite company partners in this section under the subheading "Satellite Company Collaborations".

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

Our partnerships fall into several categories, including pharmaceutical alliances and licenses, satellite company collaborators, external project funding alliances, and technology and intellectual property sales and licensing. We highlight our traditional partnering alliances and our preferred partner transactions below in more detail in this section under the subheading "Pharmaceutical Alliances and Licensing".

Pharmaceutical Alliances and Licensing

We have a long history of establishing alliances with pharmaceutical industry leaders. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, and build a broad base of license fees, milestone payments, profit share and royalty income. In contrast, our preferred partner transactions provide us with a vested partner early in the development of a drug. With our preferred partners, we are able to expand and broaden our drug discovery efforts to new disease targets in therapeutic areas that are outside of our expertise or in areas where our partners will provide tools and resources that will complement our drug discovery efforts. For instance, we established a broad strategic alliance with Biogen Idec that pairs Biogen Idec's extensive resources and expertise in neurological diseases with our antisense technology. Together we plan to create a franchise of novel treatments for neurological disorders that will expand both our pipeline and Biogen Idec's pipeline of promising new treatments. In cancer, we are working with our partner, AstraZeneca, to conduct a comprehensive clinical program for ISIS-STAT3$_{Rx}$, an anti-cancer drug we licensed to AstraZeneca. We also have a second drug in development, ISIS-AR$_{Rx}$, with AstraZeneca. Because ISIS-AR$_{Rx}$ can inhibit the production of all known forms of androgen receptor, or AR, we believe that this drug has the potential to be an effective treatment for all stages of prostate cancer, including prostate cancer patients who are resistant to current therapies. AstraZeneca plans to evaluate ISIS-AR$_{Rx}$ in AR-related cancers in a broad clinical program. Through our collaboration, we are also applying AstraZeneca's proprietary preclinical cancer models and screening systems to evaluate new oncology targets.

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

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ for the treatment of cancer and an option to license up to three cancer drugs under a separate research program. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from this collaboration. Under the terms of the agreement, we received $31 million in upfront and near-term payments comprised of a $25

million upfront payment we received in December 2012 and a $6 million payment we received in June 2013, of which we recognized $11.5 million upon receipt of the payments. We are recognizing the remaining $19.5 million as follows:

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

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic HCC. We are concurrently completing a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. In June 2013, we earned a $10 million milestone payment when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. If AstraZeneca successfully develops ISIS-STAT3$_{Rx}$, ISIS-AR$_{Rx}$, and three drugs under the research program, we could receive substantive milestone payments of more than $970 million, including up to $315.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We will earn the next milestone payment of $15 million if AstraZeneca initiates a Phase 1 study for ISIS-AR$_{Rx}$.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment, which we are amortizing through December 2015. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.2 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.25 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive up to double-digit royalties on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

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

Biogen Idec

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

ISIS-SMN$_{Rx}$

In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We received an upfront payment of $29 million, which we are amortizing through August 2016. We are eligible to receive a license fee, milestone payments and up to double-digit royalties on any product sales of ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities.

We are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants with SMA. In January 2014, we and Biogen Idec amended the original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. We and Biogen Idec added a new open—label extension study, which is being offered to those children with SMA who have completed dosing in our previous studies, and expanded the dosing in the Phase 2 study in infants with SMA. In addition, we increased the number of patients to be included in the Phase 3 studies. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by nearly $35 million. Under the terms of the amended agreement, we are eligible to receive up to $303.8 million in a license fee and payments, including $78.8 million in milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones.

As of December 31, 2013, we had earned $7 million in milestone payments for advancing the ISIS-SMN$_{Rx}$ Phase 2 program. In addition, based on the further advancement of ISIS-SMN$_{Rx}$ Phase 2 program, Biogen Idec will pay us $9.3 million in the first quarter of 2014. We will earn the next milestone payment of $18 million if we dose the first patient in the Phase 3 study in infants with SMA, which is designed to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe.

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ISIS-DMPK$_{Rx}$

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of DM1, ISIS-DMPK$_{Rx}$. We are responsible for global development of the drug through the completion of a Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments. In October 2013, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study on ISIS-DMPK$_{Rx}$, and we are eligible to receive up to another $49 million in milestone payments associated with the development of ISIS-DMPK$_{Rx}$ prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $14 million if we initiate a Phase 1 study for ISIS-DMPK$_{Rx}$.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We could receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last six years, and may be extended for any drug development programs being pursued under the collaboration. Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

If an antisense molecule is chosen for drug discovery and development of a neurological disease, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments for each antisense drug developed under the collaboration. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130

million for the achievement of regulatory milestones. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. In addition, we are eligible to receive double-digit royalties on any product sales of antisense drugs developed under this collaboration. If other modalities, such as small molecules or monoclonal antibodies are chosen, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of any drugs using other modalities developed under this collaboration. We could earn the next milestone payment of up to $10 million if we choose a target to advance under this collaboration.

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

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Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. In addition to a $15 million upfront fee, we earned $8 million in milestone payments related to the development of BMS-PCSK9$_{Rx}$. The collaboration ended in December 2011, and we regained the rights to discover and develop antisense drugs to target PCSK9. During 2013, 2012 and 2011, we earned revenue of $188,000, $290,000 and $2.4 million, respectively, from Bristol-Myers Squibb.

Eli Lilly and Company

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

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

- Eli Lilly and Company may license ISIS-EIF4E$_{Rx}$ on the predefined terms;
- Eli Lilly and Company may tell us it is not interested in licensing ISIS-EIF4E$_{Rx}$, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner; or
- Eli Lilly and Company may offer to license ISIS-EIF4E$_{Rx}$ on terms that are lower than the predefined terms, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Eli Lilly and Company.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of KYNAMRO. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to KYNAMRO, including the key product related patents described in the “Patents and Proprietary Rights” section under “ApoB 100 and KYNAMRO” on page 37 of this report, and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apo-B by binding to the mRNA encoding apo-B, throughout the world.

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

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

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

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

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

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

During 2013, 2012 and 2011, we earned revenue of $32.5 million, $67.6 million, and $72.3 million, respectively, from our relationship with Genzyme, which represented 22 percent, 66 percent, and 73 percent, respectively, of our total revenue for those years.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, for up to six programs, using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when GSK expanded the collaboration. We are amortizing these payments through July 2015.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR$_{Rx}$. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, which we are amortizing through July 2015. We also received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$ and a $2 million milestone payment in December 2013 for advancing the ongoing Phase 2/3 study of ISIS-TTR$_{Rx}$. We have earned $24.0 million primarily in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$ and we are eligible to earn an additional $46 million in pre-licensing milestone payments associated with the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, under the amended agreement, GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR$_{Rx}$ receive marketing approval and meet pre-agreed sales targets.

Our strategic alliance currently includes five active programs including the ISIS-TTR$_{Rx}$ program. We are eligible to receive on average up to $20 million in milestone payments through Phase 2 proof-of-concept for each program, except the ISIS-TTR$_{Rx}$ program, which we describe above. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept for a license fee. If GSK exercises its option to a program it will be responsible for all further development and commercialization of the program. In September 2013, we designated ISIS-GSK3$_{Rx}$ as an additional development candidate under our collaboration with GSK. ISIS-GSK3$_{Rx}$ is an antisense drug designed to inhibit the production of an undisclosed target to treat a common viral infection. To date, we have earned $10 million in milestone payments associated with advancing the ISIS-GSK3$_{Rx}$ program including a $3 million milestone payment we earned in November 2013 when we initiated a Phase 1 study for ISIS-GSK3$_{Rx}$. In November 2013, we designated ISIS-GSK4$_{Rx}$ as an additional development candidate under our collaboration with GSK and earned a $5 million milestone payment. ISIS-GSK4$_{Rx}$ is an antisense drug we designed to treat an undisclosed ocular disease. Under our agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of nearly $1.2 billion, including up to $185.5 million for the achievement of development milestones, up to $526.5 million for the achievement of regulatory milestones and up to $445 million for the achievement of commercialization milestones. We will earn the next $1 million milestone payment if we initiate an open-label extension study of ISIS-TTR$_{Rx}$. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During 2013, 2012 and 2011, we earned revenue of $35.3 million, $8.2 million and $17.7 million, respectively, from our relationship with GSK, which represented 24 percent, eight percent and 18 percent, respectively, of our total revenue for those years.

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Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein. During 2013, we earned revenue of $5.1 million from our relationship with Roche.

Satellite Company Collaborations

Through our satellite company collaborations, we expand the reach and potential of RNA-targeting therapeutics into disease areas that are outside of our core focus and advance certain RNA-targeting therapeutic technologies. We refer to these companies as our satellite companies, and this strategy as our

satellite company strategy. These relationships provide us with partners who are focused in a particular disease area and who share the common goal of advancing our drugs. In these partnerships, we typically own equity in the company, often as part of the licensing agreement and we also retain the potential to earn milestone payments and royalties.

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

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

Achaogen, Inc.

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

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have received $3 million from Achaogen, $500,000 of which was in Achaogen securities, as Achaogen has advanced plazomicin in development. In addition, assuming Achaogen successfully develops and commercializes the first two drugs under our agreement, we may receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $4 million if Achaogen initiates a Phase 3 study for plazomicin. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Achaogen. At December 31, 2013 and 2012, we owned less than 10 percent of Achaogen's equity.

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Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In 2013, we earned a $750,000 milestone payment when Alnylam initiated a Phase 3 study for a drug targeting TTR. We will earn the next milestone payment of $375,000 if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

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

We have the potential to earn sublicense revenue and a portion of milestone payments and royalty payments that Alnylam receives from licenses of our technology it grants to its partners. To date, we have earned a total of $40.5 million from Alnylam resulting from licenses of our technology for the development of RNAi therapeutics and technology that we granted to Alnylam and Alnylam has granted to its partners. We are also eligible to receive $7.5 million related to Alnylam's recently announced collaboration with Genzyme upon the closing of Alnylam's sale of stock to Genzyme

During 2013, 2012 and 2011, we earned revenue from our relationship with Alnylam totaling $1.5 million, $2.7 million and $375,000, respectively.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is developing ATL1102 for the treatment of multiple sclerosis. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103. At December 31, 2013 and 2012, we owned less than 10 percent of ATL's equity. During 2013 and 2012, we did not earn any revenue from our relationship with ATL. During 2011, we earned revenue of $210,000 from our relationship with ATL for manufacturing services we provided.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of UC and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity.

Under the agreement, we could receive substantive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $600,000 if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international Named Patient Supply regulations for patients with inflammatory bowel disease, or IBD, for which we receive royalties.

In 2010 and 2013, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we agreed to receive equity for the royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity payments we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of the equity payments is uncertain. At December 31, 2013 and 2012, we owned approximately 12 percent and 11 percent, respectively, of Atlantic Pharmaceuticals' equity. We earned $671,000 related to royalties and sales of drug substance in 2013 but because the payments were made in equity, we did not record any revenue. During 2012, we earned $3,000 related to royalties and during 2011 we did not earn any revenue from our relationship with Atlantic Pharmaceuticals.

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

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

In December 2011, Pfizer Inc. acquired Excaliard. To date, we have received $6.5 million and we are eligible to receive up to an additional $8.4 million in payments upon achievement of various milestones associated with the clinical and commercial progress of EXC 001. In addition, assuming Pfizer Inc. successfully develops and commercializes EXC 001, we may receive substantive milestone payments totaling up to $47.7 million for the achievement of key development and regulatory milestones, including up to $7.7 million for the achievement of development milestones and up to $40 million for the achievement of regulatory milestones. We will earn the next milestone payment of $1.5 million upon initiation of a Phase 3 study for EXC 001. We are also eligible to receive royalties on any product sales of EXC 001.

At December 31, 2013, we owned no equity in Excaliard. During 2013, 2012 and 2011, we received $844,000, $1.3 million and $4.4 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard and the advancement of EXC 001, which we recorded as investment gains. We did not earn any revenue during 2013, 2012 and 2011 from our relationship with Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007. iCo is developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy and is currently evaluating it in a Phase 2 study in patients with diabetic retinopathy. We received a $500,000 upfront fee from iCo and may receive substantive milestone payments totaling up to $48.4 million for the achievement of development and regulatory milestones for multiple indications, including up to $7.9 million for the achievement of development milestones and up to $40.5 million for the achievement of regulatory milestones. We will receive the next milestone payment of $4 million if iCo initiates a Phase 3 study for iCo-007. In addition, we are eligible to receive royalties on any product sales of iCo-007. Under the terms of the agreement, iCo is solely responsible for the development and commercialization of the drug. Over the course of our relationship, iCo has paid us in a combination of cash, common stock and convertible notes. During 2013, we sold a portion of the iCo stock we own resulting in aggregate net cash proceeds of $490,000. As a result, our ownership in iCo at December 31, 2013 and 2012 was approximately six percent and nine percent, respectively. During 2013 and 2012 we did not earn any revenue from our relationship with iCo and during 2011 we earned $7,000 from our relationship with iCo.

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

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

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

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

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

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us substantive milestone payments totaling up to $3.5 million for the achievement of development and regulatory milestones, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225. As of December 31, 2013, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $500,000 if OncoGenex initiates a Phase 2 study for OGX-225.

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

During 2011, we earned $750,000 in revenue from our relationship with OncoGenex. During 2013 and 2012, we did not earn any revenue from our relationship with OncoGenex.

Regulus Therapeutics Inc.

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

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new biomarker tool for characterizing diseases. Regulus focuses its drug discovery and development efforts in numerous therapeutic areas, including cancer, fibrosis, atherosclerosis and viral infections, such as Hepatitis C virus, and currently has two drugs in clinical development. Regulus is developing RG-101, an anti-miR that targets microRNA-122, for the treatment of HCV infection, and plans to initiate a Phase 1 study for RG-101 in 2014. Regulus is also developing RG-012, an anti-miR that targets microRNA-21, for the treatment of Alport Syndrome. Regulus currently plans to develop RG-012 to proof-of-concept. At that stage of development, Regulus' partner, Sanofi, has an exclusive option to license. We are eligible to receive a portion of all milestone payments Regulus receives from Sanofi if Sanofi chooses to exercise its option to license RG-012 from Regulus and RG-012 advances in development. We are also eligible to receive royalties on any future product sales of both of these drugs.

In October 2012, Regulus completed an IPO, in which we participated by purchasing $3 million of Regulus' common stock at the offering price. We remain a significant shareholder with approximately seven million shares. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. In the fourth quarter of 2012, we recorded an $18.4 million gain because of the increase in Regulus' valuation resulting from its IPO.

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

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

million, of the $25 million upfront payment and are eligible to receive 7.5 percent of all future milestone payments, in addition to royalties on any product sales. During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Regulus.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for anemia of chronic disorders, or ACD. 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. Because repayment of the promissory note was uncertain, we did not record any revenue from the upfront payment when we entered into the agreement. In May 2012, Xenon selected XEN701, a drug designed to inhibit the production of hepcidin, as a development candidate. In June 2013, we earned a $2 million license fee when Xenon exercised its option to an exclusive worldwide license to XEN701. In addition, in June 2013 Xenon repaid the $1.5 million convertible promissory note. We recognized the $2 million license fee and the $1.5 million upfront payment as revenue in the second quarter of 2013. In the first quarter of 2014, Xenon decided to discontinue development of XEN701. As a result, we will regain the rights to discover and develop antisense drugs to target hemojuvelin and hepcidin. During 2013, 2012 and 2011, we earned revenue of $3.5 million, $84,000 and $80,000, respectively, from our relationship with Xenon.

External Project Funding

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

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. In 2013, we made two payments to CHDI totaling $3 million associated with the progression of our Huntington's disease program, which we recorded as research and development expense. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI. During 2013, 2012 and 2011, we earned revenue of $414,000, $2.0 million and $2.4 million, respectively, from our relationship with CHDI.

The Ludwig Institute; Center for Neurological Studies

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

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Technology and Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We believe our patent estate represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our pharmaceutical and satellite company partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc. To date, we have generated $410 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

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

Abbott Molecular Inc.

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

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2013, 2012 and 2011, we did not earn any revenue from our relationship with AMI.

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

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases. Pfizer Inc. markets Macugen outside of the United States and Valeant markets the drug in the United States. In February 2012, Eyetech was acquired by Valeant Pharmaceuticals International, Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us for the achievement of pre-specified events and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in payments, and this license may also generate additional payments aggregating up to $2.8 million for the achievement of specified regulatory events with respect to the use of Macugen for each additional therapeutic indication. In 2013, 2012 and 2011, we earned $362,000, $499,000 and $790,000, respectively, of revenue related to royalties for Macugen under this license.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. In April 2011, we expanded our relationship with Roche Molecular Systems by granting Roche Molecular Systems a non-exclusive license to additional technology for research and diagnostic uses. During 2013, 2012 and 2011, we earned revenue of $618,000, $1.0 million and $828,000, respectively, from our relationship with Roche Molecular Systems.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Idera under which we acquired an exclusive license to all of Idera's antisense chemistry and delivery technology related to our second generation antisense drugs and to double-stranded siRNA therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense its technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of RNase H patents. During 2013, 2012 and 2011, we earned revenue of $10,000 for each period from our relationship with Idera.

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University of Massachusetts

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

Verva Pharmaceuticals Ltd.

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

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $600,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive in consideration for sublicensing the Cold Spring Harbor Laboratory's technology and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

Manufacturing

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

Due to the growing numbers of our antisense drug development partners and the clinical successes of our antisense drugs, including KYNAMRO, in 2009 we increased our manufacturing capacity by upgrading and optimizing the efficiency of our manufacturing facility. Our drug substance manufacturing facility is located in an approximately 28,704 square foot building in Carlsbad, California. We lease this building under a lease that has an initial term ending on December 31, 2031 with an option to extend the lease for up to four additional five-year periods. In addition, we have an approximately 25,792 square foot building that houses support functions for our manufacturing activities. We lease this facility under a lease that has an initial term ending in June 2021 with an option to extend the lease for up to two additional five-year periods. Our manufacturing facility is subject to periodic inspection by the FDA to ensure that it is operating in compliance with current Good Manufacturing Practices, or cGMP, requirements.

As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Genzyme, iCo, OncoGenex, Ortho-McNeil-Janssen Pharmaceuticals, Inc., Biogen Idec and AstraZeneca.

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We believe we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs, as well as to meet our current internal research and clinical needs, including for the Phase 3 clinical trials for ISIS-TTR_{Rx}, ISIS-SMN_{Rx}, and ISIS-$APOCIII_{Rx}$. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs, including the initial launch supplies for ISIS-TTR_{Rx}, ISIS- SMN_{Rx}, and ISIS-$APOCIII_{Rx}$. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we can manufacture antisense drugs at commercially competitive prices.

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

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the United States and other countries. As of February 10, 2014, we owned or exclusively licensed approximately 1,200 issued patents worldwide. This number is lower than years past due to a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company.

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

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

Chemically Modified Nucleosides and Oligonucleotides

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

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

Antisense Drug Design Motifs

MOE Gapmers

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

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

Bicyclic Nucleoside Gapmer Oligonucleotides

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

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

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Therapeutic Methods of Treatment and Antisense Drug Sequences

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

ApoB 100 and KYNAMRO

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

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,407,943	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Methods of inhibiting expression of apoB, decreasing serum cholesterol, decreasing lipoprotein levels, decreasing serum triglycerides in a human with an antisense compound 12 to 30 nucleotide in length and 100% complementary to human apoB wherein the compound is not a ribozyme.
Australia	2002-326481	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	An isolated oligonucleotide compound 12 to 30 nucleobases in length 100% complementary to at least a 12-nucleobase portion of a nucleic acid molecule having nucleotides 151-12820 of SEQ ID 3 (apoB) which is not a ribozyme and use of such compound in therapy
Japan	4471650	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2021	Use of an antisense oligonucleotide 12 to 30 nucleobases in length and 100% complementary to human apoB having one or more modifications and inhibiting expression of apoB by at least 90% in primary hepatocytes when present at a concentration of 300 nM for preparation of a medicament for decreasing serum cholesterol, and decreasing lipoprotein levels in a human

United States	7,511,131	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2025	Antisense sequence and composition of matter of KYNAMRO
Europe	EP1569695	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
Europe	EP2336318	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
India	219847	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
Australia	2003294281	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO
South Africa	2005/03690	ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION	2023	Antisense sequence and composition of matter of KYNAMRO

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Custirsen

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

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

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

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

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

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

ISIS-SMN$_{Rx}$ is protected by a suite of patents in the United States and in Europe from generic competition in the United States until at least 2028 and in Europe until 2026. These issued patents include: (i) the Bennett patent related to methods of altering mRNA processing (i.e., splicing) with a fully-modified 2'MOE oligonucleotide, (ii) a patent licensed from the University of Massachusetts drawn to antisense compounds having the sequence of ISIS-SMN$_{Rx}$, independent of chemical modification and uses of such compounds for treating SMA, and (iii) a joint patent with Cold Spring Harbor Laboratory claiming fully-modified 2'MOE compositions targeting SMN2, including the precise composition of matter of ISIS-SMN$_{Rx}$. Those patents should protect ISIS-SMN$_{Rx}$ from generic and antisense innovator competition in the United States until at least 2028 without patent term extension. The table below lists the U.S. and European issued patents protecting ISIS-SMN$_{Rx}$:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	6,210,892	ALTERATION OF CELLULAR BEHAVIOR BY MODULATION OF MRNA PROCESSING	2018	Broad claims of altering mRNA processing with a fully-modified 2'MOE oligonucleotide.
United States	8,361,977	COMPOSITIONS AND METHODS FOR	2028	Sequence and chemistry (full 2'-MOE) of ISIS-SMN$_{Rx}$

		MODULATION OF SMN2 SPLICING		
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of ISIS-SMN$_{Rx}$
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of ISIS-SMN$_{Rx}$ (chemistry independent)
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of SMN$_{Rx}$ to alter splicing of SMN2 and/or to treat SMA

Transthyretin and ISIS-TTR$_{Rx}$

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

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

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

RNAi Motifs and Mechanisms - The Crooke Patents

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

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

Manufacturing Patents

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

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

Government Regulation

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

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

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

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

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

Competition

Our Business in General

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

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

KYNAMRO

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

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

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

Aegerion has stated that it is charging in excess of $300,000 for lomitapide per patient per year, which is significantly higher than KYNAMRO. Our partner, Genzyme, has extensive experience in bringing medicines to patients with severe and rare diseases. In the United States, Genzyme intends to capitalize on its existing sales and marketing infrastructure within specialized medical communities. In addition, with an existing global commercial infrastructure in the cardiovascular community, we believe that Sanofi and its global presence will aid in the rapid expansion of KYNAMRO into markets throughout the world.

ISIS-TTR$_{Rx}$

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

We believe that of the drugs that are in development or on the market, ISIS-TTR$_{Rx}$'s closest competitor is an oral drug, tafamadis, which is only marketed in Europe under the brand name Vyndaqel. In May 2012, the FDA rejected tafamadis for use in the United States stating that the Phase 3 study data did not show that tafamadis is effective in directly slowing the progression of FAP. We believe that based on the mechanism of our drug and our preclinical data, that ISIS-TTR$_{Rx}$ could have a significantly better therapeutic profile than tafamadis and other drugs that are earlier in development. Tafamadis was designed to stabilize the TTR tetramer structure and prohibit plaque formation. Another oral drug, diflunisal, has been shown to stabilize the TTR tetramer structure and could also offer benefit to patients with TTR amyloidosis. Diflunisal is an oral generic drug that is available in the United States and Europe for use as a non-steroidal anti-inflammatory drug. Diflunisal was tested in a Phase 3 study in patients with FAP. In this study more than half of the patients discontinued treatment and although a clinically meaningful change in disease progression was measured, all patients continued to progress in their disease. If diflunisal is successful in receiving marketing approval for TTR amyloidosis, it could compete with ISIS-TTR$_{Rx}$. In addition, Alnylam is developing RNAi molecules designed to inhibit the production of TTR and recently started a Phase 3 program for its drug candidate, patisiran, in patients with FAP. If Alnylam's drug candidates are successful in clinical studies and receive marketing approval, they could compete with ISIS-TTR$_{Rx}$.

ISIS-APOCIII$_{Rx}$

We have completed a broad Phase 2 program on our novel triglyceride-lowering drug, ISIS-APOCIII$_{Rx}$, and we plan to initiate a Phase 3 program on this drug in 2014. ISIS-APOCIII$_{Rx}$ is in development to treat patients with severely high to extremely high triglyceride levels. Current triglyceride-lowering therapies, including niacin, fibrates and fish oils, are often inadequate in these patients. Our plan is to develop ISIS-APOCIII$_{Rx}$ to treat patients with severely high triglycerides, including FCS patients, who are unable to adequately reduce their triglyceride levels to acceptable levels with current therapies. Based on our Phase 2 data, we believe that ISIS-APOCIII$_{Rx}$ will work equally well as a single agent or in combination with other triglyceride-lowering drugs on the market. As such, we do not intend to displace any existing therapy with ISIS-APOCIII$_{Rx}$.

There are several drugs in development to reduce triglyceride levels in patients with severely high triglycerides. The most advanced of these drugs is pradigastat, a drug in Phase 3 development in patients with FCS. Although the Phase 2 data for pradigastat showed effective lowering of triglycerides in patients, the high incidence of gastrointestinal side effects observed could limit the drugs' tolerability. If pradigastat is successful in clinical studies and receives marketing approval this oral drug could compete with ISIS-APOCIII$_{Rx}$. CAT-2003 is an oral drug in Phase 2 development to treat patients with FCS, or extremely high triglycerides. Based on the mechanism of action of CAT-2003, we believe CAT-2003 is likely to have an effect only in a small subset of FCS patients. As such, if CAT-2003 is successful in clinical studies and receives marketing approval, we believe it could compete with ISIS-APOCIII$_{Rx}$ only in patients with severely elevated triglyceride levels, which is the second indication we plan to pursue for ISIS-APOCIII$_{Rx}$.

ISIS-SMN$_{Rx}$

In 2014, we plan to begin a Phase 3 program on ISIS-SMN$_{Rx}$ in both infants with type 1 SMA and in children with type 2 and type 3 SMA. SMA is a rare genetic disease for which there is no approved therapy on the market. Current treatment for patients with SMA is palliative and focuses on helping to maintain respiratory health. We plan to develop ISIS-SMN$_{Rx}$ to treat all forms of SMA. There are a small number of therapeutic programs designed to treat SMA that are in earlier stages of development compared to ISIS-SMN$_{Rx}$. To compete with ISIS-SMN$_{Rx}$ these therapeutic programs would need to advance into Phase 3 studies, eventually achieve marketing approval, and show a better product profile than ISIS-SMN$_{Rx}$. If those programs progress through clinical studies and the resulting drugs receive marketing approval, those drugs could compete with ISIS-SMN$_{Rx}$ as a treatment for patients with SMA.

Employees

As of February 17, 2014, we employed 304 people in all of our functions, excluding manufacturing and related departments, which employed 61 people. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of February 17, 2014:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	68	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D.	58	Director, Chief Operating Officer and Secretary
C. Frank Bennett, Ph.D.	57	Senior Vice President, Antisense Research

Richard S. Geary, Ph.D.	56	Senior Vice President, Development
Elizabeth L. Hougen	52	Senior Vice President, Finance and Chief Financial Officer
Brett P. Monia, Ph.D.	52	Senior Vice President, Drug Discovery and Corporate Development
Patrick R. O'Neil, Esq.	40	Senior Vice President, Legal and General Counsel

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

Chairman, Chief Executive Officer and President

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

B. LYNNE PARSHALL, J.D.

Director, Chief Operating Officer and Secretary

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

C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

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

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

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

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ELIZABETH L. HOUGEN

Senior Vice President, Finance and Chief Financial Officer

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

BRETT P. MONIA, Ph.D.

Senior Vice President, Drug Discovery and Corporate Development

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

PATRICK R. O'NEIL, Esq.

Senior Vice President, Legal and General Counsel

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

Item 1A. Risk Factors

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

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

Risks Associated with our Drug Discovery and Development Business

If the market does not accept KYNAMRO or our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, we are not likely to generate revenues or become consistently profitable.

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

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

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

The degree of market acceptance for KYNAMRO, and any of our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;

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- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx,}$ unaffordable.

If our drug discovery and development business fails to compete effectively, our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, will not contribute significant revenues.

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

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

These competitive developments could make our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, obsolete or non-competitive.

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

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

Regarding KYNAMRO, some competitors are pursuing a development or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion Pharmaceuticals, Inc. received approval from the FDA and the European Medicines Agency to market its MTP

inhibitor, lomitapide, as an adjunct to a low-fat diet and other lipid-lowering treatments in patients with HoFH. Our revenues and financial position will suffer if KYNAMRO cannot compete effectively in the marketplace.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, drugs like tafamadis, diflunisal, and patisiran could compete with ISIS-TTR_{Rx}, drugs like pradigastat and CAT-2003 could compete with ISIS-$APOCIII_{Rx}$, and the early development programs designed to treat patients with SMA could compete with ISIS-SMN_{Rx}.

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KYNAMRO is, and, following approval any of our other drugs, including ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, could be, subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Even if approved, we or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO, ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}.

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

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

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

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

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

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

We entered into this collaboration primarily to:

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

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

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

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

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If we or our partners fail to obtain regulatory approval for our drugs, including additional approvals for KYNAMRO or initial approvals for ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved in additional markets outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, before 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. It is possible that other regulatory agencies will not approve KYNAMRO or any of our other drugs including, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$ for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States or initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs. There are ongoing clinical studies for KYNAMRO and sales to patients, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

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

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

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

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

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Any failure or delay in the clinical studies, including any further studies under the development program for KYNAMRO and the Phase 3 studies for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, could reduce the commercial potential or viability of our drugs.

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

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

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

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including any expanded product label for KYNAMRO and initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2013, we had an accumulated deficit of approximately $967.6 million and stockholders' equity of approximately $378.4 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

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

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

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

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

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

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

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

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

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones for additional approvals or sales expectations of KYNAMRO or milestones related to the Phase 3 programs for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, the price of our securities could decrease.

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

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

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

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

From time to time we have to defend our intellectual property rights. In the event of an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in September 2011 we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California, and in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. These lawsuits may be costly and may not be resolved in our favor.

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

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of December 31, 2013, we had cash, cash equivalents and short-term investments equal to $656.8 million. If we do not meet our goals to successfully commercialize KYNAMRO or our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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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, 2013, the market price of our common stock ranged from $10.36 to $42.69 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

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

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

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

We depend on Regulus for development of our microRNA technology.

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 10, 2014, we occupied three buildings in Carlsbad, California totaling approximately 231,000 square feet of laboratory, manufacturing and office space. Our facilities include a 176,000 square foot facility that we use for our primary research and development activities, a 28,704 square foot manufacturing facility and a 25,792 square foot building adjacent to our manufacturing facility. Our 28,704 square foot facility houses manufacturing suites for our drug development business built to meet cGMP requirements and our 25,792 square foot facility has laboratory and office space

that we use to support our manufacturing activities. We lease all three buildings under lease agreements. The leases on our 176,000 square foot facility and our 28,704 square foot manufacturing facility expire in 2031 and have four five-year options to extend. Under these lease agreements, we have the option to purchase the facilities, independent of each other at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. The lease for our 25,792 square foot facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods. We believe our existing facilities are adequate for our requirements in the foreseeable future and that we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs, including for the Phase 3 clinical trials for ISIS-TTR$_{Rx}$, ISIS-SMN$_{Rx}$, and APOCIII$_{Rx}$.

Item 3. Legal Proceedings

Santaris Litigation

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion, and the case is proceeding.

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Gilead Litigation

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

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

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

	HIGH	LOW
2013		
First Quarter	$ 19.53	$ 10.36
Second Quarter	$ 28.66	$ 15.92
Third Quarter	$ 39.83	$ 23.63
Fourth Quarter	$ 42.69	$ 29.41
2012		
First Quarter	$ 9.28	$ 7.08
Second Quarter	$ 12.00	$ 7.02
Third Quarter	$ 15.61	$ 11.45
Fourth Quarter	$ 14.36	$ 7.56

As of February 21, 2014, there were approximately 719 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

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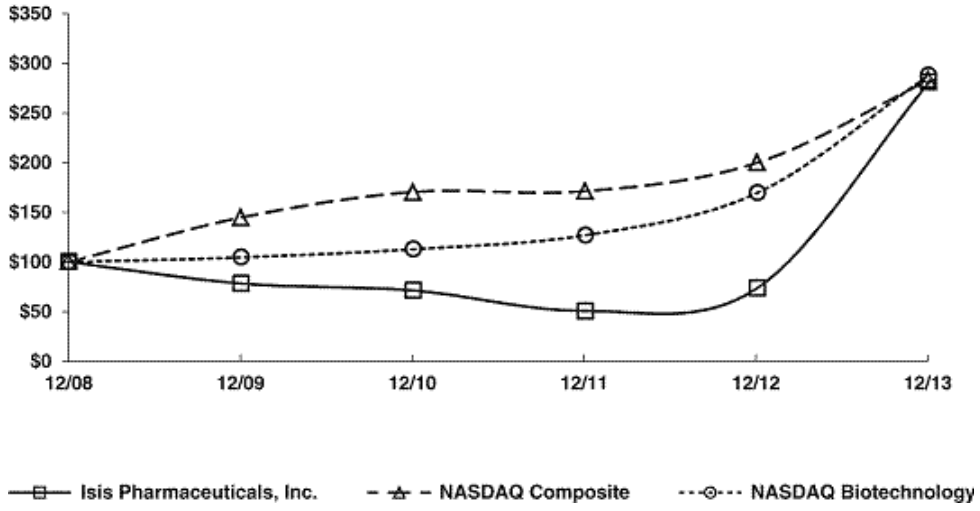
Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2008 in our common stock, the NASDAQ Composite Index (total return) and the NASDAQ Biotechnology Index. The total return assumes reinvestment of dividends.

Performance Graph (1)

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



	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13
Isis Pharmaceuticals, Inc.	$ 100	$ 78.35	$ 71.37	$ 50.85	$ 73.62	$ 280.96
NASDAQ Composite Index	$ 100	$ 144.88	$ 170.58	$ 171.30	$ 199.99	$ 283.39
NASDAQ Biotechnology Index	$ 100	$ 104.67	$ 112.89	$ 127.04	$ 169.50	$ 288.38

(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.

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Item 6. Selected Financial Data

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

	Years Ended December 31,				
	2013	2012	2011	2010	2009
Consolidated Statement of Operations Data:					
Revenue	$ 147,285	$ 102,049	$ 99,086	$ 108,473	$ 121,600
Research, development and patent expenses	$ 184,033	$ 158,458	$ 157,397	$ 145,160	$ 134,623
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (60,644)	$ (65,478)	$ (84,801)	$ (61,251)	$ (30,562)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (60,644)	$ (65,478)	$ (84,801)	$ (61,251)	$ 155,066
Basic and diluted net loss per share from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.55)	$ (0.65)	$ (0.85)	$ (0.62)	$ (0.31)
Basic and diluted net income (loss) per share attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.55)	$ (0.65)	$ (0.85)	$ (0.62)	$ 1.58
Shares used in computing basic and diluted net income (loss) per share	110,502	100,576	99,656	99,143	98,109

	As of December 31,				
	2013	2012	2011	2010	2009
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments(1)	$ 656,761	$ 374,446	$ 343,664	$ 472,353	$ 574,312
Working capital(1)	$ 637,698	$ 349,116	$ 284,027	$ 377,247	$ 484,682
Investment in Regulus Therapeutics Inc.(1)	$ 52,096	$ 33,622	$ —	$ —	$ —
Total assets(1)	$ 847,156	$ 545,686	$ 484,894	$ 550,477	$ 657,184
Long-term debt and other obligations, less current portion(1)	$ 370,954	$ 288,598	$ 232,924	$ 199,175	$ 243,675
Accumulated deficit(1)	$ (967,610)	$ (906,966)	$ (841,488)	$ (756,687)	$ (696,150)
Noncontrolling interest in Regulus Therapeutics Inc.(1)	$ —	$ —	$ —	$ —	$ 10,343
Investment in Regulus Therapeutics Inc.(1)	$ —	$ —	$ 4,424	$ 870	$ —
Stockholders' equity	$ 378,390	$ 182,766	$ 171,434	$ 244,542	$ 302,065

(1) Beginning in the first quarter of 2010, we adopted a new accounting standard and changed our method of accounting for our variable interest in Regulus. We adopted the new standard on a prospective basis; therefore, beginning in the first quarter of 2010, we deconsolidated Regulus from our consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Under the equity method of accounting, we stopped including Regulus' revenue and operating expenses in our operating results. Instead we included our share

of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our consolidated balance sheet, we presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." In October 2012, Regulus completed an IPO and we began accounting for our investment in Regulus at fair value because our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. 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.*in the notes to the Consolidated Financial Statements.

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

Overview

We are the leading company in antisense drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including severe and rare, cardiovascular, neurologic and metabolic diseases and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs.

Our flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the U.S. Food and Drug Administration, or FDA, approved the marketing application for KYNAMRO for patients with HoFH. Genzyme, a Sanofi Company, has also obtained marketing approval in other countries, including Mexico, Argentina and South Korea, and is pursuing marketing approval in other countries. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and is leveraging this expertise to reach patients with HoFH, who are in desperate need of new treatment options. Genzyme is concentrating marketing and sales efforts on lipid specialists, and physicians who refer HoFH patients to these specialists, to reach patients with HoFH in the United States and other countries.

To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at an optimal time to maximize the near- and long-term value for each drug. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of smaller companies that can exploit our drugs and technology. We call these smaller companies our satellite companies. We benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. We also maintain our broad RNA technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnership strategy, which allow us to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated six new partnerships that involve antisense drugs for the treatment of neurological diseases or cancer, including four strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. We have received more than $230 million in upfront payments and have the potential to earn nearly $6 billion in future milestone payments and licensing fees from these partnerships. In addition, we have the potential to earn nearly $3 billion in future milestone payments and licensing fees from our other partnered programs. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements. Since 2007, our partnerships have generated an aggregate of more than $1.1 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding.

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As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated $410 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Business Segments

We operate in a single segment, Drug Discovery and Development operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. In our Drug Discovery and Development operations we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. With our proprietary drug discovery platform we can

rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. When we combine this efficiency with our rational approach to selecting disease targets we can build a large and diverse portfolio of drugs to treat a variety of health conditions, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer.

Critical Accounting Policies

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

The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature;

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

Research and development revenue under collaborative agreements

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services. Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a standalone basis. We use the following hierarchy of values to

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estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

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

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

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

We determined that the initial allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

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

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

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

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

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment for the ISIS-STAT3$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $750,000, from the amount we recorded.

Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations is difficult to estimate. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize in future periods. For example, in 2013 we adjusted the period of performance on our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration with Biogen Idec. As a result of adding two new development candidates, ISIS-GSK3$_{Rx}$ and ISIS-GSK4$_{Rx}$,to our collaboration with GSK, our period of performance was extended beyond our initial estimate. Therefore, we extended the amortization period to correspond to the new extended period of performance. Similarly, with our ISIS-SMN$_{Rx}$ collaboration, we extended the amortization period to correspond to the expansion of the Phase 3 study in infants with SMA. Since we extended the amortization period for our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration, the amortization from the upfront payments for these collaborations will be $2.6 million less in 2014 compared to 2013.

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012 we have entered into four collaboration agreements with Biogen Idec:

- In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

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

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All four of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

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

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

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

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

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

- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

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

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

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

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

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with Biogen Idec, we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we provide access to our technology to Alnylam Pharmaceuticals, Inc. to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. In evaluating if a milestone is substantive we consider whether:

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

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. We consider milestone payments related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. All of the milestone payments we earned in 2013 were substantive. Therefore, we recognized the entire amount of those milestone payments in 2013, including a $25 million milestone payment from Genzyme we recognized in the first quarter of 2013 when the FDA approved the KYNAMRO NDA. Further information about our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Licensing and royalty revenue

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

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Valuation of Investments

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

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in a publicly-held biotechnology company; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

As of December 31, 2012, we classified the fair value measurements of our investment in the equity securities of Regulus and Sarepta Therapeutics, Inc. as Level 3. We calculated a lack of marketability discount on the fair value of these securities because there were restrictions on when we could trade the securities. In the first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. In the fourth quarter of 2013, we re-classified our investment in Regulus to a Level 1 investment because we are no longer subject to contractual trading restrictions on the Regulus shares we own.

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

During 2013, we recognized a $2.4 million net gain on investments primarily consisting primarily of the $1.1 million gain we realized when we sold the stock we held in Sarepta Therapeutics, Inc., the $490,000 gain we realized when we sold a portion of the stock we hold in iCo Therapeutics Inc., and the $844,000 payment we received from Pfizer, Inc. related to its acquisition of Excaliard Pharmaceuticals, Inc. During 2012 we recognized a $1.5 million net gain on investments primarily consisting of the $1.3 million payment we received from Pfizer, Inc. related to its acquisition of Excaliard. See further discussion about our investment in Excaliard in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

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

Valuation of Long-Lived Assets

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

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;
- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and
- Challenges or potential challenges to our existing patents, the likelihood that the United States Patent and Trademark Office, or foreign equivalent, will issue an application and the scope of our issued patents.

We recorded a charge of $6.4 million, $825,000 and $1.9 million for the years ended December 31, 2013, 2012 and 2011, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values. In 2013, we conducted a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. As a result, our write-downs were more significant than in prior years. We expect write-downs in future years to be similar to years prior to 2013.

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

Convertible Debt

We account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. We determine the carrying amount of the liability

component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

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

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Results of Operations

Years Ended December 31, 2013 and December 31, 2012

Revenue

Total revenue for the year ended December 31, 2013 was $147.3 million compared to $102.0 million for 2012. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. In 2013, we earned $83 million in revenue from milestone and licensing payments including:

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

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

Research and Development Revenue Under Collaborative Agreements

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

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2013 was $3.1 million and decreased compared to $5.6 million for 2012. The decrease was primarily due to $750,000 in sublicensing revenue that we earned from Alnylam in 2013 compared to $2.7 million we earned from Alnylam in 2012. In January 2014, Alnylam announced a collaboration with Genzyme, for which we are eligible to receive $7.5 million upon the closing of Alnylam's sale of stock to Genzyme under that collaboration.

Operating Expenses

Operating expenses for the year ended December 31, 2013 were $199.0 million compared to $171.0 million for 2012. The increase in operating expenses was primarily due to higher costs associated with the maturation and expansion of our pipeline. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research, Development and Patent Expenses

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

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

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

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For the year ended December 31, 2013, we incurred total research, development and patent expenses of $174.4 million compared to $151.2 million for 2012. Research, development and patent expenses in 2013 were higher primarily due to higher development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials, including advancing ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$ to the point where each is poised to begin Phase 3 studies. We also initiated numerous clinical studies and added new drugs to our pipeline. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

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

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

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

	Year Ended December 31,	
	2013	2012
Antisense drug discovery expenses	$ 42,402	$ 34,035
Non-cash compensation expense related to equity awards	2,878	2,108
Total antisense drug discovery	$ 45,280	$ 36,143

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

Antisense Drug Development

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

	Year Ended December 31,	
	2013	2012
KYNAMRO	$ 8,040	$ 10,920
ISIS-TTR$_{Rx}$	5,247	6,137
Other antisense development products	55,819	48,154
Development overhead costs	8,689	5,350
Non-cash compensation expense related to equity awards	3,202	2,482
Total antisense drug development	$ 80,997	$ 73,043

Antisense drug development expenditures were $77.8 million for the year ended December 31, 2013 compared to $70.6 million for 2012. The higher expenses in 2013 were primarily due to an increase in development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials, including advancing ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$ to the point where each is poised to begin Phase 3 studies. The increase associated with these activities was offset, in part, by lower development expenses related to KYNAMRO and ISIS-TTR$_{Rx}$. We initiated a Phase 2/3 clinical study of ISIS-TTR$_{Rx}$ in February 2013, for which we incurred a significant portion of the start-up expenses in 2012. We expect expenses for this study to increase as the study progresses. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, such as our planned Phase 3 studies for ISIS-SMN$_{Rx}$ and ISIS-APOCIII$_{Rx}$, the costs of development should increase. All amounts exclude non-cash compensation expense related to equity awards.

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We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. We and Genzyme share development costs equally until KYNAMRO is profitable.

Manufacturing and Operations

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

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

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

Manufacturing and operations expenses for the year ended December 31, 2013 were $20.5 million, and increased slightly compared to $19.2 million for 2012, primarily because we manufactured more drug product due to the maturation and expansion of our pipeline. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

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

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

	Year Ended December 31,	
	2013	2012
Personnel costs	$ 9,571	$ 9,231
Occupancy	6,897	6,909
Patent expenses	10,321	3,868
Depreciation and amortization	2,464	3,129
Insurance	1,108	1,143
Other	3,293	3,104
Non-cash compensation expense related to equity awards	2,298	1,657
Total R&D support costs	$ 35,952	$ 29,041

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R&D support costs for the year ended December 31, 2013 were $33.7 million compared to $27.4 million for 2012. Expenses increased in 2013 compared to the same period in 2012 primarily due to non-cash charges for patents and patent applications that we wrote off in 2013 due to a careful restructuring of our patent portfolio to focus our resources on patents and new patent applications that drive value for our company. All amounts exclude non-cash compensation expense related to equity awards.

General and Administrative Expenses

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

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

	Year Ended December 31,	
	2013	2012
General and administrative expenses	$ 13,173	$ 11,190
Non-cash compensation expense related to equity awards	1,745	1,325
Total general and administrative	$ 14,918	$ 12,515

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

Equity in Net Loss of Regulus Therapeutics Inc.

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

Investment Income

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

Interest Expense

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

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

	Year Ended December 31,	
	2013	2012
Convertible Notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 6,758	$ 9,845
Interest expense payable in cash	5,534	4,306
Non-cash interest expense for long-term financing liability	6,568	6,502
Other	495	498
Total interest expense	$ 19,355	$ 21,152

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Interest expense for year ended December 31, 2013 was $19.4 million compared to $21.2 million in 2012. The decrease in interest expense was primarily due to a decrease in amortization of the debt discount related to our convertible notes. We record non-cash amortization of the debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature. This means we record our convertible notes at a discount that we amortize over the life of the notes as non-cash interest expense. We are using an eight percent borrowing rate for the $2^{3}/_{4}$ percent convertible senior notes compared to a 9.3 percent borrowing rate for the $2^{5}/_{8}$ percent convertible subordinated notes that we redeemed in September 2012. The borrowing rate for our $2^{3}/_{4}$ percent notes is less than the rate for our $2^{5}/_{8}$ percent notes because of market conditions at the time of each issuance. As a result, we are amortizing less debt discount for the $2^{3}/_{4}$ percent notes compared to the $2^{5}/_{8}$ percent notes. This decrease is partially offset by an increase in interest expense payable in cash because the interest rate is slightly higher on our $2^{3}/_{4}$ percent notes compared to our $2^{5}/_{8}$ percent notes.

Gain on Investments, Net

Net gain on investments for the year ended December 31, 2013 was $2.4 million compared to $1.5 million for 2012. The net gain on investments in 2013 was primarily due to the $1.1 million gain we realized when we sold the stock we held in Sarepta Therapeutics, Inc., the $490,000 gain we realized when we sold a portion of the stock we hold in iCo Therapeutics Inc., and the $844,000 payment we received from Pfizer, Inc. related to its acquisition of Excaliard Pharmaceuticals, Inc. During 2012 we recognized a $1.5 million net gain on investments primarily consisting of the $1.3 million payment we received from Pfizer, Inc. related to its acquisition of Excaliard. These gains demonstrate the value that we are realizing from our satellite company strategy. See further discussion about our investments in Excaliard and iCo Therapeutics Inc. in Note 7, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Early Retirement of Debt

Loss on early retirement of debt for the year ended December 31, 2012 was $4.8 million, reflecting the early redemption of our $2^{5}/_{8}$ percent convertible notes in the second half of 2012. We did not recognize any loss on early retirement of debt in 2013.

Income Tax Benefit

In 2013, we recorded a tax benefit of $5.9 million, which reflected our application of the intraperiod tax allocation rules under which we are required to record a tax benefit in continuing operations to offset the tax provision we recorded directly to other comprehensive income primarily related to unrealized gains on our equity investments in our satellite companies, including Regulus. Our income tax benefit declined from $9.1 million in 2012 because the unrealized gains in 2013 were not as large as in 2012.

Net Loss and Net Loss Per Share

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

- $18.4 million gain we realized in 2012 because of the increase in Regulus' valuation resulting from its IPO; and
- $4.8 million loss, $3.6 million of which was non-cash, we recorded in 2012 on the early retirement of our $2^{5}/_{8}$% convertible subordinated notes.

Net Operating Loss Carryforward

At December 31, 2013, we had federal and California tax net operating loss carryforwards of approximately $685.8 million and $894.9 million, respectively. We also had federal and California research credit carryforwards of approximately $62.6 million and $22.2 million, respectively. Our federal and California tax loss carryforwards expire at various dates starting in 2014, unless we use them before then. Our net operating loss and tax credit carryforwards may be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions

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

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Years Ended December 31, 2012 and December 31, 2011

Revenue

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

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the year ended December 31, 2012 was $96.4 million compared to $96.2 million for 2011. In 2012, we recognized revenue from new sources in connection with our collaboration with AstraZeneca, our three new collaborations with Biogen Idec and the KYNAMRO FDA acceptance milestone from Genzyme. At the same time, in 2012, revenue from amortization of the upfront payments associated with the Genzyme collaboration ended as planned in mid-2012.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2012 was $5.6 million compared to $2.9 million for 2011. The increase was primarily due to $2.7 million in sublicensing revenue that we earned from Alnylam in 2012.

Operating Expenses

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

Research, Development and Patent Expenses

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

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

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

For the year ended December 31, 2012, we incurred total research, development and patent expenses of $151.2 million compared to $148.9 million for 2011. Research, development and patent expenses in 2012 were slightly higher primarily due to higher development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO. All amounts exclude non-cash compensation expense related to equity awards.

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Antisense Drug Discovery

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

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

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

Antisense Drug Development

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

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

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

Manufacturing and Operations

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

	Year Ended December 31,	
	2012	2011
Manufacturing and operations	$ 19,232	$ 19,506
Non-cash compensation expense related to equity awards	999	1,101
Total manufacturing and operations	$ 20,231	$ 20,607

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

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R&D Support

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

	Year Ended December 31,	
	2012	2011
Personnel costs	$ 9,231	$ 8,665
Occupancy	6,909	9,446
Patents	3,868	4,306
Depreciation and amortization	3,129	4,032
Insurance	1,143	884
Other	3,104	2,591
Non-cash compensation expense related to equity awards	1,657	2,085
Total R&D support costs	$ 29,041	$ 32,009

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

General and Administrative Expenses

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

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

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

Equity in Net Loss of Regulus Therapeutics Inc.

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

In the fourth quarter of 2012, we recorded an $18.4 million gain because of the increase in Regulus' valuation resulting from its IPO. We have reflected this gain in a separate line on our Consolidated Statements of Operations called "Gain on investment in Regulus Therapeutics Inc." Also, in the fourth quarter of 2012 we stopped using the equity method of accounting for our equity investment in Regulus and instead we began accounting for our investment at fair value.

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Investment Income

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

Interest Expense

Interest expense for the year ended December 31, 2012 totaled $21.2 million compared to $16.7 million for 2011. The increase in interest expense in 2012 is primarily a result of additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility. The increase is also due to higher interest expense for our convertible notes because in 2012 we used the proceeds from our $2^{3}¤_{4}$ convertible notes to redeem the entire outstanding amount of our $2^{5}¤_{8}$ percent convertible notes. See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information about our convertible notes and long-term liability for our primary research and development facility.

Gain on Investments, Net

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

Early Retirement of Debt

In September 2012, we redeemed our $2^{5}/_{8}$ percent convertible subordinated notes. The carrying value of the $2^{5}/_{8}$ percent notes on our balance sheet included a discount based on the estimated fair value of similar debt instruments without the conversion feature. We were amortizing this discount over the expected life of the debt as additional non-cash interest expense. As a result of our early redemption of the $2^{5}/_{8}$ percent notes, we recognized a $4.8 million loss primarily related to a non-cash write-off of the unamortized portion of the debt discount and debt issuance costs. See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for additional information about our redemption of the $2^{5}/_{8}$ percent notes.

Income Tax Benefit

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

Net Loss and Net Loss Per Share

Net loss for the year ended December 31, 2012 was $65.5 million compared to $84.8 million for 2011. Basic and diluted net loss per share for the year ended December 31, 2012 was $0.65 per share compared to $0.85 per share for 2011. Our net loss for 2012 was significantly lower than 2011 primarily due to the $18.4 million gain from our investment in Regulus and the related $9.1 million income tax benefit offset, in part, by an increase in our net operating loss, the $4.8 million loss on the early retirement of our $2^{5}¤_{8}$ percent convertible subordinated notes, additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility, and slightly higher interest expense related to our convertible notes.

Net Operating Loss Carryforward

At December 31, 2012, we had federal and California tax net operating loss carryforwards of approximately $636.9 million and $561.2 million, respectively. We also had federal and California research credit carryforwards of approximately $44.2 million and $18.4 million, respectively.

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Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2013, we have earned approximately $1.3 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through December 31, 2013, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $786.9 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2013, we had cash, cash equivalents and short-term investments of $656.8 million and stockholders' equity of $378.4 million. In comparison, we had cash, cash equivalents and short-term investments of $374.4 million and stockholders' equity of $182.8 million at December 31, 2012. We received a substantial amount of cash in 2013, including:

- $225 million in payments from our partners;
- $173 million in net proceeds from a public offering of our common stock; and
- $63 million in proceeds from stock option exercises.

At December 31, 2013, we had consolidated working capital of $637.7 million compared to $349.1 million at December 31, 2012. The significant increase in our working capital in 2013 was primarily due to the cash we received in 2013 from our partners and the issuance of our common stock as well as an increase in the carrying value of our investment in Regulus.

As of December 31, 2013, our debt and other obligations totaled $283.5 million compared to $284.1 million at December 31, 2012. The decrease was primarily due to rent and principal payments we made in 2013 on our lease obligations and notes payable, partially offset by $2.5 million we drew down in June 2013 on our equipment financing arrangement. See Note 4, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

The following table summarizes our contractual obligations as of December 31, 2013. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2¾ percent Convertible Senior Notes (principal and interest payable)	$ 234.5	$ 5.5	$ 11.1	$ 11.1	$ 206.8
Facility Rent Payments	$ 137.9	$ 6.2	$ 12.7	$ 13.5	$ 105.5
Equipment Financing Arrangements (principal and interest payable)	$ 7.8	$ 4.4	$ 3.4	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Capital Lease	$ 0.4	$ 0.2	$ 0.2	$ —	$ —
Operating Leases	$ 26.4	$ 1.5	$ 2.9	$ 2.9	$ 19.1
Total	$ 408.3	$ 17.9	$ 30.4	$ 27.6	$ 332.4

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

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

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

In October 2008, we entered into an equipment financing loan agreement and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.39 percent. As of December 31, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.28 percent and we can borrow up to an additional $3.4 million in principal until April 2014 to finance the

purchase of equipment. The carrying balance under this loan agreement at December 31, 2013 and 2012 was $7.5 million and $10.0 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

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

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2013 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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

Item 8. Financial Statements and Supplementary Data

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

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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 2013 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

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

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2013.

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2013, we assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting established in the 1992 "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission, under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on that assessment, our management concluded that we maintained effective internal control over financial reporting as of December 31, 2013.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2013, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

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

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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, 2013, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (1992 framework) (the COSO criteria). Isis Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

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

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

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

In our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2013, 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, 2013 and 2012, and the related statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2013 of Isis Pharmaceuticals, Inc. and our report dated February 28, 2014 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2014

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Item 9B. Other Information

On January 27, 2014, we entered into a Letter Agreement Amendment with Biogen Idec, which amended the clinical development plan for ISIS-SMN_{Rx} to add a new open-label extension study for those children with SMA who have completed dosing in our previous studies, to expand the dosing in the Phase 2 study in infants with SMA, and to increase the number of patients to be included in the Phase 3 studies. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration.

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 25, 2014 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2014 Annual Meeting of Stockholders to be held on June 10, 2014.

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 8-K filed on December 9, 2013. Our Code of Ethics and Business Conduct is posted on our website at www.isispharma.com. We intend to disclose future amendments to, or waivers from, our Code of Ethics and Business Conduct on our website.

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, 2013.

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)	7,078,280	$ 12.11	5,715,176(c)
Equity compensation plans not approved by stockholders(b)	630,086	$ 14.84	—
Total	7,708,366	$ 12.33	5,715,176

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

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

(c) Of these shares, 264,275 remained available for purchase under the ESPP as of December 31, 2013. 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.

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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, 2013, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 630,086 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 4,906,111 shares under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

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

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

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or

- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

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

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

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

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Item 14. Principal Accounting 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, 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 82.

(b) Exhibits

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

(c) Financial Statement Schedules

None.

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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, 2014.

ISIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke and Elizabeth L. Hougen, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 28, 2014
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer and Secretary	February 28, 2014
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 28, 2014
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 28, 2014
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	February 28, 2014
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 28, 2014
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	February 28, 2014
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 28, 2014
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 28, 2014

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INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006. (2)
3.3	Amended and Restated Bylaws. (13)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock. (12)
4.2	Specimen Common Stock Certificate. (1)
4.3	Stock Purchase Agreement between the Registrant and Genzyme Corporation dated January 7, 2008. (5)
4.4	Indenture, dated as of August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2 ¾ percent Convertible Senior Note due 2019. (30)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule. (37)
10.2*	Registrant's 1989 Stock Option Plan, as amended. (27)
10.3*	Registrant's Amended and Restated Employee Stock Purchase Plan. (15)
10.4	Form of Employee Assignment of Patent Rights. (1)
10.5*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement. (7)
10.6	Drug Development and License Option Agreement dated December 2, 2009 between the Registrant and Eli Lilly and Company. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (24)
10.7	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (6)
10.8	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (14)
10.9	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008. Portions of this

exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (9)

10.10 Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (10)

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

10.12 Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (24)

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10.13 Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (17)

10.14 Lease Agreement between the Registrant and BMR-Gazelle Court LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (25)

10.15 Second Amendment to Lease Agreement dated May 15, 2011 between the Registrant and BMR-Gazelle Court LLC, with First Amendment to Lease Agreement included. (10)

10.16 Registrant's Amended and Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 12, 2013. (34)

10.17* Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. (27)

10.18* Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement. (21)

10.19* Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. (32)

10.20* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. (16)

10.21* Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and B. Lynne Parshall. (16)

10.22 Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 between the Registrant and Alnylam Pharmaceuticals, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (20)

10.23* Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (19)

10.24 Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc. (23)

10.25* Form of Option Agreement for Options granted under the 2011 Equity Incentive Plan. (29)

10.26* Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan. (29)

10.27 Second Amendment to Lease Agreement between the Registrant and BMR-2282 Faraday Avenue LLC dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (25)

10.28* Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan. (11)

10.29* Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan. (11)

10.30* Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan. (11)

10.31 Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (25)

10.32 First Amendment to Loan Agreement between the Registrant and RBS Asset Finance, Inc. dated September 30, 2009. (24)

10.33 Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC. (18)

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10.34 Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (23)

10.35	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (3)
10.36	Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated January 1, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (4)
10.37	Amendment No. 1 to Amended and Restated License Agreement between the Registrant and OncoGenex Technologies Inc. dated December 18, 2009. (24)
10.38	Amendment Number One to the Amended and Restated License and Collaboration Agreement dated June 10, 2010 among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (26)
10.39	Second Amendment to Loan Agreement dated November 15, 2010 between the Registrant and RBS Asset Finance, Inc. (22)
10.40	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (31)
10.41	Third Amendment to Loan Agreement dated June 24, 2012 between the Registrant and RBS Asset Finance, Inc. (32)
10.42	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (32)
10.43	Letter Agreement Amendment between the Registrant and Alnylam Pharmaceuticals, Inc. dated August 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (33)
10.44	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (37)
10.45	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (37)
10.46	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (37)
10.47	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (35)
10.48	Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (35)
10.49	Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated September 5, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)

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10.50	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)
10.51	Amendment Number Three to the Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated August 2, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. (34)
14.1	Registrant’s Code of Ethics and Business Conduct. (36)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney. (28)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

99.2	Form of Confidentiality Agreement. (8)
101	The following financial statements from the Isis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2013, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of stockholders' equity, (iv) consolidated statements of cash flows, and (v) notes to consolidated financial statements (detail tagged).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(28) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2013, reference is made to page 81.

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

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

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

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

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

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

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

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

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

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

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ISIS PHARMACEUTICALS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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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, 2013 and 2012, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2013. 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, 2013 and 2012, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2013, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2013, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (1992 framework) and our report dated February 28, 2014 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2014

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

	December 31, 2013	December 31, 2012
ASSETS		
Current assets:		
Cash and cash equivalents	$ 159,973	$ 124,482
Short-term investments	496,788	249,964
Contracts receivable	11,102	522
Inventories	8,033	6,121
Investment in Regulus Therapeutics Inc.	52,096	33,622
Other current assets	7,518	8,727
Total current assets	735,510	423,438
Property, plant and equipment, net	86,198	91,084
Licenses, net	4,572	6,579
Patents, net	15,517	18,646
Deposits and other assets	5,359	5,939
Total assets	$ 847,156	$ 545,686
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 11,009	$ 10,239
Accrued compensation	12,168	7,878
Accrued liabilities	22,092	15,401
Current portion of long-term obligations	4,408	4,879
Current portion of deferred contract revenue	48,135	35,925
Total current liabilities	97,812	74,322
Long-term deferred contract revenue	142,790	66,656
2¾ percent convertible senior notes	150,334	143,990
Long-term obligations, less current portion	6,542	7,402
Long-term financing liability for leased facility	71,288	70,550
Total liabilities	468,766	362,920
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 116,471,371 and 101,481,134 shares issued and outstanding at December 31, 2013 and 2012, respectively	116	102
Additional paid-in capital	1,324,804	1,077,150
Accumulated other comprehensive income	21,080	12,480
Accumulated deficit	(967,610)	(906,966)
Total stockholders' equity	378,390	182,766
Total liabilities and stockholders' equity	$ 847,156	$ 545,686

See accompanying notes.

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

	Years Ended December 31, 2013	2012	2011
Revenue:			
Research and development revenue under collaborative agreements	$ 144,194	$ 96,415	$ 96,190
Licensing and royalty revenue	3,091	5,634	2,896
Total revenue	147,285	102,049	99,086
Expenses:			
Research, development and patent expenses	184,033	158,458	157,397
General and administrative	14,918	12,515	12,789
Total operating expenses	198,951	170,973	170,186
Loss from operations	(51,666)	(68,924)	(71,100)

Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	—	(1,406)	(3,554)
Investment income	2,085	1,844	2,414
Interest expense	(19,355)	(21,152)	(16,732)
Gain on investments, net	2,378	1,465	4,182
Gain on investment in Regulus Therapeutics Inc.	—	18,356	—
Loss on early retirement of debt	—	(4,770)	—
Loss before income tax benefit (expense)	(66,558)	(74,587)	(84,790)
Income tax benefit (expense)	5,914	9,109	(11)
Net loss	$ (60,644)	$ (65,478)	$ (84,801)
Basic and diluted net loss per share	$ (0.55)	$ (0.65)	$ (0.85)
Shares used in computing basic and diluted net loss per share	110,502	100,576	99,656

See accompanying notes.

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

	Years Ended December 31,		
	2013	2012	2011
Net loss	$ (60,644)	$ (65,478)	$ (84,801)
Unrealized gains (losses) on investments, net of tax	10,253	13,250	(1,719)
Reclassification adjustment for realized gains included in net loss	(1,653)	—	—
Comprehensive loss	$ (52,044)	$ (52,228)	$ (86,520)

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2013, 2012 and 2011
(In thousands)

	Isis Pharmaceuticals, Inc. Stockholders' Equity					
	Common stock		Additional paid in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total stockholders' equity
Description	Shares	Amount				
Balance at December 31, 2010	99,394	$ 99	$ 1,000,181	$ 949	$ (756,687)	$ 244,542
Net loss	—	—	—	—	(84,801)	(84,801)
Change in unrealized gains (losses), net of tax	—	—	—	(1,719)	—	(1,719)
Issuance of common stock in connection with employee stock plans	646	1	3,566	—	—	3,567
Warrants exercised	3	—	—	—	—	—
Share-based compensation expense	—	—	9,845	—	—	9,845
Balance at December 31, 2011	100,043	$ 100	$ 1,013,592	$ (770)	$ (841,488)	$ 171,434
Net loss	—	—	—	—	(65,478)	(65,478)
Change in unrealized gains (losses), net of tax	—	—	—	13,250	—	13,250
Issuance of common stock in connection with employee stock plans	1,438	2	9,468	—	—	9,470
2⅝ percent convertible subordinated notes redemption, equity portion	—	—	(12,041)	—	—	(12,041)
2¾ percent convertible senior	—	—	57,560	—	—	57,560

notes, equity portion, net of issuance costs						
Share-based compensation expense	—	—	8,571	—	—	8,571
Balance at December 31, 2012	101,481	$ 102	$ 1,077,150	$ 12,480	$ (906,966)	$ 182,766
Net loss	—	—	—	—	(60,644)	(60,644)
Change in unrealized gains (losses), net of tax	—	—	—	8,600	—	8,600
Issuance of common stock in connection with employee stock plans	5,372	5	62,953	—	—	62,958
Issuance of public common stock	9,618	9	173,283	—	—	173,292
Share-based compensation expense	—	—	11,418	—	—	11,418
Balance at December 31, 2013	116,471	$ 116	$ 1,324,804	$ 21,080	$ (967,610)	$ 378,390

See accompanying notes.

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

	Years Ended December 31,		
	2013	2012	2011
Operating activities:			
Net loss	$ (60,644)	$ (65,478)	$ (84,801)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	6,591	7,074	6,594
Amortization of patents	1,184	1,224	1,938
Amortization of licenses	2,007	2,457	3,252
Amortization of premium on investments, net	5,572	4,193	5,410
Amortization of debt issuance costs	415	619	507
Amortization of 2⅝ percent convertible subordinated notes discount	—	6,169	8,553
Amortization of 2¾ percent convertible senior notes discount	6,344	2,268	—
Amortization of long-term financing liability for leased facility	6,567	6,503	2,872
Share-based compensation expense	11,418	8,571	9,845
Equity in net loss of Regulus Therapeutics Inc.	—	1,406	3,554
Gain on investment in Regulus Therapeutics Inc.	—	(18,356)	—
Loss on early retirement of debt	—	4,770	—
Gain on investments, net	(2,378)	(1,465)	(4,182)
Non-cash losses related to patents, licensing and property, plant and equipment	6,306	825	1,924
Tax benefit from other unrealized gains on securities	(5,914)	(9,111)	—
Changes in operating assets and liabilities:			
Contracts receivable	(10,580)	6,399	(5,679)
Inventories	(1,912)	(1,982)	(1,655)
Other current and long-term assets	(1,091)	279	914
Accounts payable	66	1,292	875
Accrued compensation	4,290	(1,305)	2,352
Deferred rent	217	255	382
Accrued liabilities	6,691	(3,254)	6,273
Deferred contract revenue	88,344	48,523	(70,857)
Net cash provided by (used in) operating activities	63,493	1,876	(111,929)
Investing activities:			
Purchases of short-term investments	(425,554)	(217,877)	(371,108)
Proceeds from the sale of short-term investments	172,762	242,659	488,918
Purchases of property, plant and equipment	(1,552)	(1,479)	(10,203)
Acquisition of licenses and other assets, net	(3,810)	(3,691)	(3,667)
Investment in Regulus Therapeutics Inc.	—	(3,000)	—
Purchases of strategic investments	—	(790)	(359)
Proceeds from the sale of strategic investments	2,428	2,177	4,445
Net cash (used in) provided by investing activities	(255,726)	17,999	108,026
Financing activities:			
Proceeds from equity awards	62,958	9,470	3,567
Proceeds from issuance of 2¾ percent convertible senior notes, net of issuance costs	—	194,697	—
Principal and premium payment on redemption of the 2⅝ percent convertible subordinated notes	—	(163,718)	—
Proceeds from public common stock offering	173,292	—	—
Proceeds from equipment financing arrangement	2,513	9,100	1,625
Principal payments on debt and capital lease obligations	(11,039)	(10,419)	(5,864)

Net cash provided by (used in) financing activities	227,724	39,130	(672)
Net increase (decrease) in cash and cash equivalents	35,491	59,005	(4,575)
Cash and cash equivalents at beginning of year	124,482	65,477	70,052
Cash and cash equivalents at end of year	$ 159,973	$ 124,482	$ 65,477

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

Supplemental disclosures of cash flow information:			
Interest paid	$ 6,000	$ 5,770	$ 4,804
Income taxes paid, net of refund received	$ 2	$ 2	$ 2
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 704	$ 647	$ 902
Capitalized costs and financing liability associated with leased facility	$ —	$ —	$ 59,730

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. (“we”, “us” or “our”) and our wholly owned subsidiary, Symphony GenIsis, Inc., which is currently inactive. In addition to our wholly owned subsidiary, our consolidated financial statements include our equity investment in Regulus Therapeutics Inc. In October 2012, Regulus completed an initial public offering (IPO). We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus’ operating and financial policies.

Organization and business activity

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

Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for the years ended December 31, 2013, 2012 and 2011, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 2¾ percent convertible senior notes;
- 2⅝ percent convertible subordinated notes;
- GlaxoSmithKline, or GSK, convertible promissory notes issued by Regulus;
- Dilutive stock options;
- Unvested restricted stock units; and
- Warrants issued to Symphony GenIsis Holdings LLC.

In April 2011, Symphony GenIsis Holdings LLC exercised its warrants. As a result, the Symphony GenIsis warrants were not common equivalent shares for the years ended December 31, 2013 and 2012. We redeemed all of our 2½ percent notes in September 2012 and in October 2012 Regulus completed an IPO, after which we were no longer guarantors of the two convertible notes that Regulus issued to GSK. As a result, the 2½ percent notes and GSK convertible promissory notes were not common equivalent shares for the year ended December 31, 2013.

Revenue Recognition

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

Research and development revenue under collaborative agreements

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

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price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

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

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

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

We determined that the initial allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

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

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

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

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

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment for the ISIS-STAT3$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $750,000, from the amount we recorded.

Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations is difficult to estimate. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize in future periods. For example, in 2013 we adjusted the period of performance on our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration with Biogen Idec. As a result of adding two new development candidates, ISIS-GSK3$_{Rx}$ and ISIS-GSK4$_{Rx}$, to our collaboration with GSK, our period of performance was extended beyond our initial estimate. Therefore, we extended the amortization period to correspond to the new extended period of performance. Similarly, with our ISIS-SMN$_{Rx}$ collaboration, we extended the amortization period to correspond to the expansion of the Phase 3 study in infants with SMA. Since we extended the amortization period for our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration, the amortization from the upfront payments for these collaborations will be $2.6 million less in 2014 compared to 2013.

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012 we have entered into four collaboration agreements with Biogen Idec:

- In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for Spinal Muscular Atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen Idec to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

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

All four of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen Idec agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

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

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

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

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

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

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

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

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

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

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with Biogen Idec, we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we provide access to our technology to Alnylam Pharmaceuticals, Inc. to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. In evaluating if a milestone is substantive we consider whether:

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

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. We consider milestone payments related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. All of the milestone payments we earned in 2013 were substantive. Therefore, we recognized the entire amount of those milestone payments in 2013,

including a $25 million milestone payment from Genzyme we recognized in the first quarter of 2013 when the FDA approved the KYNAMRO NDA. Further information about our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

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

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Research, development and patent expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our consolidated balance sheet and we expense them as the services are provided. For the years ended December 31, 2013, 2012 and 2011, research and development expenses were $173.7 million, $154.6 million and $153.1 million, respectively. A portion of the costs included in research and development expenses are costs associated with our collaboration agreements. For the years ended December 31, 2013, 2012 and 2011, research and development costs of approximately $51.9 million, $39.0 million, and $26.3 million, respectively, were related to our collaborative research and development arrangements.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents and amortize these costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 9.8 years at December 31, 2013.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2013 and 2012 was $24.9 million and $31.4 million, respectively. Accumulated amortization related to patents was $9.4 million and $12.8 million at December 31, 2013 and 2012, respectively. Based on existing patents, estimated amortization expense related to patents in each of the next five years is as follows:

Years Ending December 31,	Amortization (in millions)
2014	$ 1.0
2015	$ 0.9
2016	$ 0.9
2017	$ 0.8
2018	$ 0.7

We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs. In 2013, 2012 and 2011, patent expenses were $10.3 million, $3.9 million and $4.3 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $6.4 million, $817,000 and $1.9 million, respectively.

Concentration of credit risk

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

Cash, cash equivalents and short-term investments

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

We have equity investments in privately- and publicly-held biotechnology companies that we have received as part of a technology license or collaboration agreement. At December 31, 2013 we held ownership interests of less than 20 percent in each of the respective companies.

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

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

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the years ended December 31, 2013, 2012 or 2011. Total inventory, which consisted of raw materials, was $8.0 million and $6.1 million as of December 31, 2013 and 2012, respectively.

Property, plant and equipment

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

	December 31,	
	2013	2012
Equipment and computer software	$ 44,698	$ 44,109
Building and building systems	48,132	48,120
Land improvements	2,846	2,849
Leasehold improvements	35,282	34,931
Furniture and fixtures	5,473	5,342
	136,431	135,351
Less accumulated depreciation	(60,431)	(54,465)
	76,000	80,886
Land	10,198	10,198
	$ 86,198	$ 91,084

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

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

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

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Licenses

We obtain licenses from third parties and capitalize the costs related to exclusive licenses. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately five years and 15 years. The cost of our licenses at December 31, 2013 and 2012 was $36.2 million. Accumulated amortization related to licenses was $31.6 million and $29.6 million at December 31, 2013 and 2012, respectively. Based on existing licenses, estimated amortization expense related to licenses is as follows:

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

Fair value of financial instruments

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

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and exclusive licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of

such assets. We recorded a charge of $6.4 million, $825,000 and $1.9 million for the years ended December 31, 2013, 2012 and 2011, respectively, related primarily to the write-down of intangible assets.

Equity method of accounting

We accounted for our ownership interest in Regulus using the equity method of accounting until Regulus' IPO in October 2012. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. See Note 3, *Investments*, for additional information regarding our fair value accounting for our investment in Regulus. Under the equity method of accounting, we included our share of Regulus' operating results on a separate line in our consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc."

Use of estimates

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

Reclassifications

We have reclassified certain prior period amounts to conform to the current period presentation. Certain amounts previously reported as research and development revenue have been reclassified to licensing and royalty revenue to conform to the current period presentation.

Consolidation of variable interest entities

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of December 31, 2013 and 2012, we had collaborative arrangements with five and six entities, respectively, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have the power to direct the activities that most significantly impact the economic performance of our variable interest entities, the obligation to absorb losses, or the right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. As of December 31, 2013, the total carrying value of our investments in variable interest entities was $53.4 million, and was primarily related to our investment in Regulus. Our maximum exposure to loss related to these variable interest entities is limited to the carrying value of our investments.

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Stock-based compensation

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

We use the Black-Scholes model as our method of valuing option awards and stock purchase rights under the ESPP. On the grant date, we use our stock price and assumptions regarding a number of highly complex and subjective variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although we determine the estimated fair value of employee stock options using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

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

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

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

Accumulated other comprehensive income (loss)

Accumulated other comprehensive income (loss) is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income (loss) to our consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the years ended December 31, 2013, 2012 and 2011 (in thousands):

	Year Ended December 31,		
	2013	2012	2011
Beginning balance accumulated other comprehensive income (loss)	$ 12,480	$ (770)	$ 949
Other comprehensive income (loss) before reclassifications, net of tax (1)	10,253	13,250	(1,719)

Amounts reclassified from accumulated other comprehensive income (2)	(1,653)	—	—
Net current period other comprehensive income (loss)	8,600	13,250	(1,719)
Ending balance accumulated other comprehensive income (loss)	$ 21,080	$ 12,480	$ (770)

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

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

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Convertible debt

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

Segment information

We operate in a single segment, Drug Discovery and Development operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment.

Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. Our Level 3 investments include investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the years ended December 31, 2013 and 2012 there were no transfers between our Level 1 and Level 2 investments. We use the end of reporting period method for determining transfers between levels.

We measure the following major security types at fair value on a recurring basis. We break down the inputs used to measure fair value for these assets at December 31, 2013 and 2012 as follows (in thousands):

	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,357	$ 133,233	$ 13,124	$ —
Corporate debt securities (2)	394,773	—	394,773	—
Debt securities issued by U.S. government agencies (2)	64,432	—	64,432	—
Debt securities issued by the U.S. Treasury (2)	15,328	15,328	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	22,255	—	22,255	—
Investment in Regulus Therapeutics Inc.	52,096	52,096	—	—
Equity securities (3)	1,276	1,276	—	—
Total	$ 696,517	$ 201,933	$ 494,584	$ —

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	At December 31, 2012	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 105,496	$ 101,496	$ 4,000	$ —
Corporate debt securities (2)	193,507	—	193,507	—
Debt securities issued by U.S. government agencies (2)	18,108	—	18,108	—
Debt securities issued by the U.S. Treasury (2)	13,452	13,452	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	24,897	—	24,897	—

Investment in Regulus Therapeutics Inc.	33,622	—	—	33,622
Equity securities (3)	4,874	4,146	—	728
Total	$ 393,956	$ 119,094	$ 240,512	$ 34,350

(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.

As of December 31, 2012, we classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc., or Sarepta, as Level 3. We calculated a lack of marketability discount on the fair value of these investments because of trading restrictions on the securities. We consider the inputs we used to calculate the lack of marketability discount Level 3 inputs and, as a result, we categorized these investments as Level 3. We determined the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ended. As of December 31, 2012, our Level 3 investments in Regulus and Sarepta had a gross fair value of $44.4 million and $1.0 million, respectively, less a lack of marketability discount of $10.8 million and $296,000, respectively, for a net carrying value of $33.6 million and $728,000, respectively. In the first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. In the fourth quarter of 2013, we re-classified our investment in Regulus to a Level 1 investment because we are no longer subject to contractual trading restrictions on the Regulus shares we own. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the years ended December 31, 2013, 2012 and 2011 (in thousands):

	Year Ended December 31,		
	2013	2012	2011
Beginning balance of Level 3 investments	$ 34,350	$ —	$ —
Purchases	—	3,040	—
Transfers into Level 3 investments	—	25,198	—
Total gains and losses:			
Included in gain on investments	(1,163)	—	—
Included in accumulated other comprehensive income	32,272	6,112	—
Transfers out of Level 3 investments	(65,419)	—	—
Cost basis of shares sold	(40)	—	—
Ending balance of Level 3 investments	$ —	$ 34,350	$ —

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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 July 2013, the FASB issued accounting guidance on the financial statement presentation of an unrecognized tax benefit when a net operating loss carryforward, a similar tax loss, or a tax credit carryforward exists. The guidance is effective prospectively for fiscal years, and interim periods within those years, beginning after December 15, 2013. We will adopt this guidance in our fiscal year beginning January 1, 2014. We do not believe the adoption of this guidance will have a material impact on our consolidated financial statements.

2. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-targeting therapeutics. We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, and certain early fundamental patents in the microRNA field.

In October 2012, Regulus completed an IPO of approximately 12.7 million shares of its common stock at $4.00 per share. As part of the offering, we purchased $3.0 million of Regulus' common stock at the offering price. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. We also recorded an $18.4 million gain in the fourth quarter of 2012 because of the increase in Regulus' valuation resulting from its IPO. We have reflected this gain in a separate line on our consolidated statement of operations called "Gain on investment in Regulus Therapeutics Inc."

3. Investments

As of December 31, 2013, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2013:

One year or less	34%
After one year but within two years	44%
After two years but within three years	22%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 78 percent of our available-for-sale securities having a maturity of less than two years.

At December 31, 2013, we had an ownership interest of less than 20 percent in each of three private companies and three public companies with which we conduct business. The privately-held companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen Inc., and Atlantic Pharmaceuticals Limited. The publicly-traded companies are Antisense Therapeutics Limited, or ATL, iCo Therapeutics Inc., and Regulus. We account for equity investments in the privately-held companies under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. In October 2012, Regulus completed an IPO and our ownership of Regulus' common stock dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. In the fourth quarter of 2012, we stopped using the equity method to account for our investment in Regulus and instead we began accounting for it at fair value.

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During 2013, we recognized a $2.4 million net gain on investments primarily consisting of the $1.1 million gain we realized when we sold all of the common stock that we held in Sarepta Therapeutics, Inc., the $490,000 gain we realized when we sold a portion of the stock we hold in iCo Therapeutics Inc., and the $844,000 payment we received from Pfizer, Inc. related to its acquisition of Excaliard Pharmaceuticals, Inc. During 2012 we recognized a $1.5 million net gain on investments primarily consisting of the $1.3 million payment we received from Pfizer, Inc. related to its acquisition of Excaliard. See further discussion about our investments in these satellite companies in Note 7, *Collaborative Arrangements and Licensing Agreements*.

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

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

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

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December 31, 2012	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					

Corporate debt securities(1)	$ 115,249	$ 81	$ (9)	$ —	$ 115,321
Debt securities issued by U.S. government agencies(1)	12,100	2	(66)	—	12,036
Debt securities issued by the U.S. Treasury	1,000	1	—	—	1,001
Debt securities issued by states of the United States and political subdivisions of the states	16,560	18	(2)	—	16,576
Total securities with a maturity of one year or less	144,909	102	(77)	—	144,934
Corporate debt securities	80,166	112	(92)	—	80,186
Debt securities issued by U.S. government agencies	8,034	38	—	—	8,072
Debt securities issued by the U.S. Treasury	12,424	27	—	—	12,451
Debt securities issued by states of the United States and political subdivisions of the states	8,306	31	(16)	—	8,321
Total securities with a maturity of more than one year	108,930	208	(108)	—	109,030
Total available-for-sale securities	$ 253,839	$ 310	$ (185)	$ —	$ 253,964

December 31, 2012	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 18,096	$ —	$ —	$ 33,622
Securities included in other current assets	1,579	4,175	—	(880)	4,874
Securities included deposits and other assets	625	—	—	—	625
Total equity securities	$ 17,730	$ 22,271	$ —	$ (880)	$ 39,121
Total available-for-sale and equity securities	$ 271,569	$ 22,581	$ (185)	$ (880)	$ 293,085

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

Investments we consider to be temporarily impaired at December 31, 2013 are as follows (in thousands):

		Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	148	$ 213,469	$ (412)	$ 8,228	$ (8)	$ 221,697	$ (420)
Debt securities issued by U.S. government agencies	8	49,437	(143)	—	—	49,437	(143)
Debt securities issued by states of the United States and political subdivisions of the states	7	6,964	(52)	4,130	(4)	11,094	(56)
Total temporarily impaired securities	163	$ 269,870	$ (607)	$ 12,358	$ (12)	$ 282,228	$ (619)

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.

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4. Long-Term Obligations and Commitments

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

	December 31, 2013	December 31, 2012
2¾ percent convertible senior notes	$ 150,334	$ 143,990
Long-term financing liability for leased facility	71,288	70,550
Equipment financing arrangement	7,461	9,993
Leases and other obligations	3,489	2,288
Total	$ 232,572	$ 226,821
Less: current portion	(4,408)	(4,879)
Total Long-Term Obligations	$ 228,164	$ 221,942

Convertible Notes

In August 2012, we completed a $201.3 million convertible debt offering, which raised net proceeds of $194.7 million, after deducting $6.6 million in issuance costs. The $201.3 million convertible senior notes mature in 2019 and bear interest at 2¾ percent, which is payable semi-annually in arrears on April 1 and October 1 of each year. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem the entire $162.5 million in principal of our $2^5/_8$ percent notes at a price of $164.0 million including accrued interest. The $162.5 million convertible subordinated notes had a maturity date of 2027 and bore interest at $2^5/_8$ percent, which was payable in cash semi-annually. We recognized a $4.8 million loss as a result of the redemption of the $2^5/_8$ percent notes. A significant portion of the loss, or $3.6 million, was non-cash and related to the unamortized debt discount and debt issuance costs and the remainder was related to a $1.2 million early redemption premium we paid to the holders of the $2^5/_8$ percent notes.

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

The price of our common stock exceeded the conversion threshold price during the quarter ended December 31, 2013. As a result, the 2¾ percent notes are convertible at the option of the holders during the quarter ending March 31, 2014. We have not received a notice of conversion and we do not believe we will receive a conversion request. As of December 31, 2013, the if-converted value of the 2¾ percent notes, which assumes that the notes will be converted into shares of our common stock, exceeded the principal amount by $281.0 million. We did not include the potential effect of the conversion of our convertible notes into our common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

We account for our convertible notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of similar debt instruments without the conversion feature and to record the remaining portion in equity. As a result, we recorded our convertible debt at a discount, which we are amortizing as additional non-cash interest expense over the expected life of the debt. We are amortizing the debt discount for our 2¾ percent notes over seven years. We were amortizing the debt discount for our 2⅝ percent notes over seven years until we redeemed the notes in September 2012. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate was eight percent and 9.3 percent for the 2¾ percent notes and 2⅝ percent notes, respectively. At December 31, 2013 the principal and accrued interest payable on the 2¾ percent notes was $202.6 million and the fair value based on quoted market prices was $505.1 million. Interest expense for the year ended December 31, 2013, 2012 and 2011 included $6.3 million, $8.4 million and $8.6 million, respectively, of non-cash interest expense related to the amortization of the debt discount for our convertible notes.

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

	December 31,	
	2013	2012
Principal amount of convertible notes outstanding	$ 201,250	$ 201,250
Unamortized portion of liability component	(50,916)	(57,260)
Long-term debt	$ 150,334	$ 143,990
Carrying value of equity component	$ 59,528	$ 59,528

Equipment Financing Arrangement

In October 2008, we entered into an equipment financing loan agreement, and in September 2009 and June 2012 we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent and in June 2013 we drew down $2.5 million in principal at an interest rate of 4.39 percent. As of December 31, 2013, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.28 percent and we can borrow up to an additional $3.4 million in principal until April 2014 to finance the purchase of equipment. The carrying balance under this loan agreement at December 31, 2013 and 2012 was $7.5 million and $10.0 million, respectively.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2013 are as follows (in thousands):

2014	$ 10,246
2015	8,544
2016	6,117
2017	5,594
2018	5,594
Thereafter	207,805
Subtotal	$ 243,900
Less: current portion	(4,408)
Less: fixed and determinable interest	(34,498)
Less: debt discount	(50,916)
Plus: Deferred rent	1,647
Total	$ 155,725

Operating Leases

We lease office and laboratory space under non-cancelable operating leases with terms through December 2031. We are located in three buildings in Carlsbad, California and occupy approximately 231,000 square feet of laboratory and office space. Our facilities include a 176,000 square foot facility that we use for our primary research and development activities, a 28,704 square foot manufacturing facility and a 25,792 square foot building adjacent to our manufacturing facility. Our 28,704 square foot facility houses manufacturing suites for our drug development business built to meet current Good Manufacturing Practices and our 25,792 square foot facility has laboratory and office space that we use to support our manufacturing activities. The lease for

our 28,704 square foot manufacturing facility expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. The lease for the 25,792 square foot facility has an initial term ending in June 2021 with an option to extend the lease for up to two five-year periods. We account for the lease of our 176,000 square foot facility as a financing obligation as discussed below. We also lease office equipment under non-cancelable operating leases with terms through June 2017.

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Annual future minimum payments under operating leases as of December 31, 2013 are as follows (in thousands):

	Operating Leases
2014	$ 1,470
2015	1,395
2016	1,538
2017	1,481
2018	1,451
Thereafter	19,126
Total minimum payments	$ 26,461

Rent expense for the years ended December 31, 2013, 2012 and 2011 was $1.8 million, $1.9 million and $4.6 million, respectively. We recognize rent expense on a straight line basis over the lease term for the lease on our manufacturing facility and the lease on our building adjacent to our manufacturing facility, which resulted in a deferred rent balance of $1.6 million and $1.4 million at December 31, 2013 and 2012, respectively.

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P., or BioMed. Under the lease, BioMed constructed our primary research and development facility in Carlsbad, California. The lease expires in 2031 and has four five-year options to extend. Under the lease agreement, we have the option to purchase the facility and land at the end of each year from 2016 through 2020, and at the end of 2026 and 2031. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, we recorded the costs for the facility as a fixed asset and we also recorded a corresponding liability in our non-current liabilities as a long-term financing obligation. In July 2011, we took possession of the facility and began depreciating the cost of the facility over its economic useful life. At December 31, 2013 and 2012, the facility and associated parcel of land had a net book value of $66.7 million and $68.9 million, respectively, which included $5.5 million and $3.2 million, respectively, of accumulated depreciation. We are applying our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In conjunction with the lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land, which requires us to account for the purchase and sale of the land as a financing transaction. As such, our property, plant and equipment at December 31, 2013 and 2012 included the value of the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease terminates.

Annual future rent payments as of December 31, 2013 for our primary research and development facility are as follows (in thousands):

	Future Rent Payments
2014	$ 6,179
2015	6,179
2016	6,550
2017	6,550
2018	6,943
Thereafter	105,508
Total minimum payments	$ 137,909

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5. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2013, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2013.

Common Stock

At December 31, 2013 and 2012, we had 200,000,000 shares of common stock authorized, of which 116,471,371 and 101,481,134 were issued and outstanding, respectively. As of December 31, 2013, total common shares reserved for future issuance were 19,810,897.

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

During the years ending December 31, 2013, 2012 and 2011, we issued 5,372,000, 1,438,000 and 646,000 shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and Employee Stock Purchase Plan, or ESPP, purchases. We received net proceeds from these transactions of $63.0 million, $9.5 million and $3.6 million in 2013, 2012 and 2011, respectively.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter. Options we granted after May 26, 2004 have a term of seven years while options we granted before May 26, 2004 have a term of ten years. At December 31, 2013, a total of 6,211,169 options were outstanding, of which options to purchase 3,033,298 shares were exercisable, and 93,378 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, 2013, a total of 630,086 options were outstanding, of which 630,086 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,

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

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards. The plan provides for the purchase of up to 5,500,000 shares of our common stock for issuance to our employees, directors, and consultants. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock units awards to our employees, directors and consultants. Under the 2011 Plan, stock options cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four year period. At December 31, 2013, a total of 407,738 options were outstanding, no shares were exercisable, and 5,046,148 shares were available for future grant under the 2011 Plan.

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

Corporate Transactions and Change in Control under 2011 Plan

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

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and

- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the 2002 Plan). The 2002 Plan provides for the purchase of up to 1,200,000 shares of our common stock to our non-employee directors. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2013, a total of 459,373 options were outstanding, 285,002 of the shares issued were exercisable and 311,375 shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 2,424,596 million shares authorized under the plan as of December 31, 2013. 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 ended on January 1, 2010. During 2013, employees purchased and we issued to employees 102,812 shares under the ESPP at $9.04 per share. At December 31, 2013, 264,275 shares were available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2013 (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, 2012	10,823	$ 11.30		
Granted	1,911	$ 15.88		
Exercised	(5,216)	$ 11.89		
Cancelled/forfeited/expired	(239)	$ 11.19		
Outstanding at December 31, 2013	7,279	$ 12.08	4.28	$ 202,078
Exercisable at December 31, 2013	3,948	$ 11.52	3.13	$ 111,685

The weighted-average estimated fair values of options granted were $7.10, $3.55 and $4.85 for the years ended December 31, 2013, 2012 and 2011, respectively. The total intrinsic value of options exercised during the years ended December 31, 2013, 2012 and 2011 were $69.6 million, $7.6 million and $686,000, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $62.0 million, $8.7 million and $2.8 million for the years ended December 31, 2013, 2012 and 2011, respectively. For the year ended December 31, 2013, the weighted-average fair value of options exercised was $25.24. As of December 31, 2013, total unrecognized compensation cost related to non-vested stock-based compensation plans was $9.6 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.1 years.

Restricted Stock Unit Activity

The following table summarizes the restricted stock unit, or RSU, activity for the year ended December 31, 2013 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2012	188	$ 8.37
Granted	297	$ 17.42
Vested	(47)	$ 16.64
Cancelled/forfeited	(13)	$ 11.78
Non-vested at December 31, 2013	425	$ 13.67

For the years ended December 31, 2013 and 2012, the weighted-average grant date fair value of RSUs granted to employees was $16.94 and $8.22 per RSU, respectively, and the weighted-average grant date fair value of RSUs granted to our Board of Directors was $27.95 and $12.94 per RSU, respectively. As of December 31, 2013, total unrecognized compensation cost related to RSUs was $3.5 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.5 years.

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Stock-based Valuation and Compensation Expense Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2013, 2012 and 2011 (in thousands), which was allocated as follows:

	Year Ended December 31,		
	2013	2012	2011
Research, development and patents	$ 9,673	$ 7,246	$ 8,527
General and administrative	1,745	1,325	1,318
Total	$ 11,418	$ 8,571	$ 9,845

Determining Fair Value

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

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

For the years ended December 31, 2013, 2012 and 2011, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2013	2012	2011
Risk-free interest rate	1.1%	1.1%	2.3%
Dividend yield	0.0%	0.0%	0.0%
Volatility	51.1%	50.7%	52.4%
Expected life	5.1 years	5.1 years	5.3 years

Board of Director Stock Options:

	December 31,		
	2013	2012	2011
Risk-free interest rate	2.2%	1.3%	2.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	52.7%	51.3%	52.8%
Expected life	7.2 years	7.6 years	7.8 years

ESPP:

	December 31,		
	2013	2012	2011
Risk-free interest rate	0.1%	0.1%	0.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	62.9%	44.5%	34.9%
Expected life	6 months	6 months	6 months

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

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

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

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. We estimated the expected term of options we have granted based on historical exercise patterns.

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

Warrants

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. In April 2011, Symphony GenIsis Holdings LLC exercised the remaining warrants and none remain outstanding.

6. Income Taxes

We have net deferred tax assets relating primarily to net operating loss carryforwards, or NOL's, and research and development tax credit carryfowards. Subject to certain limitations, we may use these deferred tax assets to offset taxable income in future periods. Since we have a history of losses and the likelihood of future profitability is not assured, we have provided a full valuation allowance for the deferred tax assets in our balance sheet as of December 31, 2013. If we determine that we are able to realize a portion or all of these deferred tax assets in the future, we will record an adjustment to increase their recorded value and a corresponding adjustment to increase income or additional paid in capital, as appropriate, in that same period.

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During 2013 and 2012, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. As a result, for the years ended December 31, 2013 and 2012, we recorded a $5.9 million and $9.1 million tax benefit, respectively, in continuing operations and a $5.9 million and $9.1 million tax expense, respectively, in other comprehensive income.

We are subject to taxation in the United States and various state jurisdictions. Our tax years for 1998 and forward are subject to examination by the U.S. tax authorities and our tax years for 1991 and forward are subject to examination by the California tax authorities due to the carryforward of unutilized net operating losses and research and development credits. Our tax years for 2006 and 2007 are currently being audited by California's Franchise Tax Board, or FTB. We do not expect that the results of these examinations will have a material effect on our financial condition or results of operations.

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

	Year Ended December 31,		
	2013	2012	2011
Current:			
Federal	$ —	$ —	$ —
State	2	2	11
Total current	2	2	11
Deferred:			
Federal	(5,082)	(7,827)	—
State	(834)	(1,284)	—
Foreign	—	—	—
Total deferred	(5,916)	(9,111)	—
Income Tax Expense (Benefit)	$ (5,914)	$ (9,109)	$ 11

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,					
	2013		2012		2011	
Pre tax loss	$ (66,558)		$ (74,587)		$ (84,790)	
Statutory rate	(23,295)	35.0%	(26,105)	35.0%	(29,677)	35.0%
State income tax net of federal benefit	(3,823)	5.7%	(4,284)	5.7%	(4,870)	5.7%
Net change in valuation allowance	28,850	(43.3)%	25,269	(33.9)%	41,136	(48.5)%
Gain on Investment in Regulus Therapeutics Inc.	—	—	(6,353)	8.5%	—	—
Tax credits	(15,839)	23.8%	806	(1.1)%	(4,202)	5.0%
Noncontrolling interest	—	—	—	—	1,448	(1.7)%
Deferred tax true-up	8,023	(12.1)%	839	(1.1)%	(4,236)	5.0%
Other	170	(0.2)%	719	(0.9)%	412	(0.5)%
Effective rate	$ (5,914)	8.9%	$ (9,109)	12.2%	$ 11	(0.0)%

Significant components of our deferred tax assets and liabilities as of December 31, 2013 and 2012 are as follows (in thousands):

	Year Ended December 31,	
	2013	2012
Deferred Tax Assets:		

Net operating loss carryovers	$ 260,462	$ 244,539
R&D credits	65,600	46,928
Capitalized R&D	2,736	22,223
Deferred revenue	28,555	7,285
Accrued restructuring	3,304	3,605
Other	7,107	18,931
Total deferred tax assets	$ 367,764	$ 343,511
Deferred Tax Liabilities:		
Convertible debt	$ (20,895)	$ (23,322)
Intangible and capital assets	(4,614)	(6,784)
Net deferred tax asset	$ 342,255	$ 313,405
Valuation allowance	(342,255)	(313,405)
Net deferreds	$ —	$ —

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The deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2013 and 2012 that arose directly from (or the use of which was postponed by) tax deductions related to equity compensation in excess of compensation recognized for financial reporting. Those deferred tax assets include non-qualified stock options and incentive stock options we issued. We will increase stockholders' equity by approximately $27.8 million if and when we ultimately realize such deferred tax assets. We use tax return ordering for purposes of determining when excess tax benefits have been realized.

At December 31, 2013, we had federal and California tax net operating loss carryforwards of approximately $685.8 million and $894.9 million, respectively. Our Federal and California tax loss carryforwards will expire at various dates starting in 2014, unless we use them before then. At December 31, 2013, we also had federal and California research and development tax credit carryforwards of approximately $62.6 million and $22.2 million, respectively. Our Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless we use them prior to expiration. Our California research and development tax credit carryforwards are available indefinitely. In 2009, we had a substantial amount of taxable income and we used a portion of our Federal NOL carryforwards to reduce our federal income taxes. We did not use any of our California NOL carryforwards to offset our state taxes in 2009 because California suspended the use of NOL carryforwards for 2009. As a result, our Federal NOL carryforwards are lower than our California NOL carryforwards.

We analyze filing positions in all of the federal and state jurisdictions where we are required to file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of being sustained.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2013	2012	2011
Beginning balance of unrecognized tax benefits	$ 10,872	$ 9,834	$ 8,968
Decrease for prior period tax positions	—	(174)	(97)
Increase for prior period tax positions	9,821	791	—
Increase for current period tax positions	3,271	421	963
Ending balance of unrecognized tax benefits	$ 23,964	$ 10,872	$ 9,834

Our unrecognized gross tax benefits presented above would not reduce our annual effective tax rate if recognized because we have recorded a full valuation allowance on our deferred tax assets. We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months. We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2013.

The American Taxpayer Relief Act of 2012, which reinstated the United States federal research and development tax credit retroactively from January 1, 2012 through December 31, 2013, was not enacted into law until the first quarter of 2013. Therefore, the expected tax benefit resulting from such reinstatement for 2012 is reflected in the Company's estimated annual effective tax rate for 2013.

7. Collaborative Arrangements and Licensing Agreements

Pharmaceutical Alliances and Licensing

AstraZeneca

In December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ for the treatment of cancer and an option to license up to three cancer drugs under a separate research program. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from this collaboration. Under the terms of the agreement, we received $31 million in upfront and near-term payments comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013, of which we recognized $11.5 million upon receipt of the payments. We are recognizing the remaining $19.5 million as follows:

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

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are concurrently completing a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. In June 2013, we earned a $10 million milestone payment when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. ISIS-AR$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. If AstraZeneca successfully develops ISIS-STAT3$_{Rx}$, ISIS-AR$_{Rx}$, and three drugs under the research program, we could receive substantive milestone payments of more than $970 million, including up to $315.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We will earn the next milestone payment of $15 million if AstraZeneca initiates a Phase 1 study for ISIS-AR$_{Rx}$.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment, which we are amortizing through December 2015. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.2 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.25 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive up to double-digit royalties on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

During 2013 and 2012, we earned revenue of $29.1 million and $9.3 million, respectively, from our relationship with AstraZeneca, which represented 20 percent and nine percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2013 and 2012 included deferred revenue of $9.3 million and $15.7 million, respectively, related to our relationship with AstraZeneca.

Biogen Idec

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

ISIS-SMN$_{Rx}$

In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We received an upfront payment of $29 million, which we are amortizing through August 2016. We are eligible to receive a license fee, milestone payments and up to double-digit royalties on any product sales of ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities.

We are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants with SMA. In January 2014, we and Biogen Idec amended the original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. We and Biogen Idec added a new open—label extension study, which is being offered to those children with SMA who have completed dosing in our previous studies, and expanded the dosing in the Phase 2 study in infants with SMA. In addition, we increased the number of patients to be included in the Phase 3 studies. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by nearly $35 million. Under the terms of the amended agreement, we are eligible to receive up to $303.8 million in a license fee and payments, including $78.8 million in milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones.

As of December 31, 2013, we had earned $7 million in milestone payments for advancing the ISIS-SMN$_{Rx}$ Phase 2 program. In addition, based on the further advancement of ISIS-SMN$_{Rx}$ Phase 2 program, Biogen Idec will pay us $9.3 million in the first quarter of 2014. We will earn the next milestone payment of $18 million if we dose the first patient in the Phase 3 study in infants with SMA, which is designed to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe.

ISIS-DMPK$_{Rx}$

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1, ISIS-DMPK$_{Rx}$. We are responsible for global development of the drug through the completion of a Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments. In October 2013, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study on ISIS-DMPK$_{Rx}$, and we are eligible to receive up to another $49 million in milestone payments associated with the development of ISIS-DMPK$_{Rx}$ prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive up to double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $14 million if we initiate a Phase 1 study for ISIS-DMPK$_{Rx}$.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We could receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we are eligible to receive double-digit royalties on any product sales of drugs resulting from each of the three programs. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen Idec gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last six years, and may be extended for any drug development programs being pursued under the collaboration. Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen Idec could potentially require us to refund.

If an antisense molecule is chosen for drug discovery and development of a neurological disease, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments for each antisense drug developed under the collaboration. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. In addition, we are eligible to receive double-digit royalties on any product sales of antisense drugs developed under this collaboration. If other modalities, such as small molecules or monoclonal antibodies are chosen, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of any drugs using other modalities developed under this collaboration. We could earn the next milestone payment of up to $10 million if we choose a target to advance under this collaboration.

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During 2013 and 2012, we earned revenue of $37.0 million and $8.5 million, respectively, from our relationships with Biogen Idec, which represented 25 percent and eight percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2013 and 2012 included deferred revenue of $145.1 million and $62.6 million, respectively, related to our relationship with Biogen Idec.

Bristol-Myers Squibb

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb to discover, develop and commercialize novel antisense drugs targeting proprotein convertase subtilisin/kexin type 9, or PCSK9. In addition to a $15 million upfront fee, we earned $8 million in milestone payments related to the development of BMS-PCSK9$_{Rx}$. The collaboration ended in December 2011, and we regained the rights to discover and develop antisense drugs to target PCSK9. During 2013, 2012 and 2011, we earned revenue of $188,000, $290,000 and $2.4 million, respectively, from Bristol-Myers Squibb. Our balance sheet at December 31, 2012 included deferred revenue of $126,000 related to our relationship with Bristol-Myers Squibb.

Eli Lilly and Company

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

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

- Eli Lilly and Company may license ISIS-EIF4E$_{Rx}$ on the predefined terms;
- Eli Lilly and Company may tell us it is not interested in licensing ISIS-EIF4E$_{Rx}$, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner; or
- Eli Lilly and Company may offer to license ISIS-EIF4E$_{Rx}$ on terms that are lower than the predefined terms, in which case we may license ISIS-EIF4E$_{Rx}$ to another partner so long as the licensing terms we reach with the new partner are better than terms offered by Eli Lilly and Company and we have not publicly disclosed any results from a new clinical study of ISIS-EIF4E$_{Rx}$ prior to reaching the agreement with the new partner.

During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Eli Lilly and Company.

Genzyme Corporation, a Sanofi company

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

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

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

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

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

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

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

During 2013, 2012 and 2011, we earned revenue of $32.5 million, $67.6 million, and $72.3 million, respectively, from our relationship with Genzyme, which represented 22 percent, 66 percent, and 73 percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2012 included deferred revenue of $3.8 million for KYNAMRO drug substance that we shipped to Genzyme in 2013.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, for up to six programs, using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. This alliance allows us to control and facilitate development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when GSK expanded the collaboration. We are amortizing these payments through July 2015.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR$_{Rx}$. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012, which we are amortizing through July 2015. We also received a $7.5 million milestone payment in February 2013 when we initiated the Phase 2/3 clinical study for ISIS-TTR$_{Rx}$ and a $2 million milestone payment in December 2013 for advancing the ongoing Phase 2/3 study of ISIS-TTR$_{Rx}$. We have earned $24.0 million primarily in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$ and we are eligible to earn an additional $46 million in pre-licensing milestone payments associated with the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, under the amended agreement, GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR$_{Rx}$ receive marketing approval and meet pre-agreed sales targets.

Our strategic alliance currently includes five active programs including the ISIS-TTR$_{Rx}$ program. We are eligible to receive on average up to $20 million in milestone payments through Phase 2 proof-of-concept for each program, except the ISIS-TTR$_{Rx}$ program, which we describe above. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept for a license fee. If GSK exercises its option to a program it will be responsible for all further development and commercialization of the program. In September 2013, we designated ISIS-GSK3$_{Rx}$ as an additional development candidate under our collaboration with GSK.

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ISIS-GSK3$_{Rx}$ is an antisense drug designed to inhibit the production of an undisclosed target to treat a common viral infection. To date, we have earned $10 million in milestone payments associated with advancing the ISIS-GSK3$_{Rx}$ program including a $3 million milestone payment we earned in November 2013 when we initiated a Phase 1 study for ISIS-GSK3$_{Rx}$. In November 2013, we designated ISIS-GSK4$_{Rx}$ as an additional development candidate under our collaboration with GSK and earned a $5 million milestone payment. ISIS-GSK4$_{Rx}$ is an antisense drug we designed to treat an undisclosed ocular disease. Under our agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of nearly $1.2 billion, including up to $185.5 million for the achievement of development milestones, up to $526.5 million for the achievement of regulatory milestones and up to $445 million for the achievement of commercialization milestones. We will earn the next $1 million milestone payment if we initiate an open-label extension study of ISIS-TTR$_{Rx}$. In addition, we are eligible to receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

During 2013, 2012 and 2011, we earned revenue of $35.3 million, $8.2 million and $17.7 million, respectively, from our relationship with GSK, which represented 24 percent, eight percent and 18 percent, respectively, of our total revenue for those years. Our balance sheets at December 31, 2013 and 2012 included deferred revenue of $11.5 million and $19.9 million, respectively, related to our relationship with GSK.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein. During 2013, we earned revenue of $5.1 million from our relationship with Roche. Our balance sheet at December 31, 2013 included deferred revenue of $25 million related to our relationship with Roche.

Satellite Company Collaborations

Achaogen, Inc.

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

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have received $3 million from Achaogen, $500,000 of which was in Achaogen securities, as Achaogen has advanced plazomicin in development. In addition, assuming Achaogen successfully develops and commercializes the first two drugs under our agreement, we may receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $4 million if Achaogen initiates a Phase 3 study for plazomicin. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Achaogen. At December 31, 2013 and 2012, we owned less than 10 percent of Achaogen's equity.

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Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In 2013, we earned a $750,000 milestone payment when Alnylam initiated a Phase 3 study for a drug targeting TTR. We will earn the next milestone payment of $375,000 if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

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

We have the potential to earn sublicense revenue and a portion of milestone payments and royalty payments that Alnylam receives from licenses of our technology it grants to its partners. To date, we have earned a total of $40.5 million from Alnylam resulting from licenses of our technology for the development of RNAi therapeutics and technology that we granted to Alnylam and Alnylam has granted to its partners. We are also eligible to receive $7.5 million related to Alnylam's recently announced collaboration with Genzyme upon the closing of Alnylam's sale of stock to Genzyme.

During 2013, 2012 and 2011, we earned revenue from our relationship with Alnylam totaling $1.5 million, $2.7 million and $375,000, respectively.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL is developing ATL1102 for the treatment of multiple sclerosis. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103. At December 31, 2013 and 2012, we owned less than 10 percent of ATL's equity. During 2013 and 2012, we did not earn any revenue from our relationship with ATL. During 2011, we earned revenue of $210,000 from our relationship with ATL for manufacturing services we provided.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006, which is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity.

Under the agreement, we could receive substantive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $600,000 if Atlantic Pharmaceuticals submits an NDA for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international Named Patient Supply regulations for patients with inflammatory bowel disease, or IBD, for which we receive royalties.

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In 2010 and 2013, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we agreed to receive equity for the royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity payments we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of the equity payments is uncertain. At December 31, 2013 and 2012, we owned approximately 12 percent and 11 percent, respectively, of Atlantic Pharmaceuticals' equity. We earned $671,000 related to royalties and sales of drug substance in 2013 but because the payments were made in equity, we did not record any revenue. During 2012, we earned $3,000 related to royalties and during 2011 we did not earn any revenue from our relationship with Atlantic Pharmaceuticals.

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

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

In December 2011, Pfizer Inc. acquired Excaliard. To date, we have received $6.5 million and we are eligible to receive up to an additional $8.4 million in payments upon achievement of various milestones associated with the clinical and commercial progress of EXC 001. In addition, assuming Pfizer Inc. successfully develops and commercializes EXC 001, we may receive substantive milestone payments totaling up to $47.7 million for the achievement of key development and regulatory milestones, including up to $7.7 million for the achievement of development milestones and up to $40 million for the achievement of regulatory milestones. We will earn the next milestone payment of $1.5 million upon initiation of a Phase 3 study for EXC 001. We are also eligible to receive royalties on any product sales of EXC 001.

At December 31, 2013, we owned no equity in Excaliard. During 2013, 2012 and 2011, we received $844,000, $1.3 million and $4.4 million, respectively, from Pfizer Inc. in payments related to the acquisition of Excaliard and the advancement of EXC 001, which we recorded as investment gains. We did not earn any revenue during 2013, 2012 and 2011 from our relationship with Excaliard.

iCo Therapeutics Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo-007. iCo is developing iCo-007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy and is currently evaluating it in a Phase 2 study in patients with diabetic retinopathy. We received a $500,000 upfront fee from iCo and may receive substantive milestone payments totaling up to $48.4 million for the achievement of development and regulatory milestones for multiple indications, including up to $7.9 million for the achievement of development milestones and up to $40.5 million for the achievement of regulatory milestones. We will receive the next milestone payment of $4 million if iCo initiates a Phase 3 study for iCo-007. In addition, we are eligible to receive royalties on any product sales of iCo-007. Under the terms of the agreement, iCo is solely responsible for the development and commercialization of the drug. Over the course of our relationship, iCo has paid us in a combination of cash, common stock and convertible notes. During 2013, we sold a portion of the iCo stock we own resulting in aggregate net cash proceeds of $490,000. As a result, our ownership in iCo at December 31, 2013 and 2012 was approximately six percent and nine percent, respectively. During 2013 and 2012 we did not earn any revenue from our relationship with iCo and during 2011 we earned $7,000 from our relationship with iCo.

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize custirsen, formerly OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we and OncoGenex amended the co-development agreement pursuant to which OncoGenex became solely

responsible for the costs, development and commercialization of custirsen. In exchange, OncoGenex agreed to pay us royalties on sales of custirsen and to share consideration it receives from licensing custirsen to a third party, except for consideration OncoGenex receives for the fair market value of equity and reimbursement of research and development expenses.

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

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

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

In August 2003, we and OncoGenex entered into a separate collaboration and license agreement for the development of a second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us substantive milestone payments totaling up to $3.5 million for the achievement of development and regulatory milestones, including up to $1.5 million for the achievement of development milestones and up to $2 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties on future product sales of OGX-225. As of December 31, 2013, OncoGenex had not achieved any milestone events related to OGX-225. We will earn the next milestone payment of $500,000 if OncoGenex initiates a Phase 2 study for OGX-225.

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

During 2011, we earned $750,000 in revenue from our relationship with OncoGenex. During 2013 and 2012, we did not earn any revenue from our relationship with OncoGenex.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. Regulus combines our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-targeting therapeutics. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner.

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new biomarker tool for characterizing diseases. Regulus focuses its drug discovery and development efforts in numerous therapeutic areas, including cancer, fibrosis, atherosclerosis and viral infections, such as Hepatitis C virus, and currently has two drugs in clinical development. Regulus is developing RG-101, an anti-miR that targets microRNA-122 for the treatment of HCV infection, and plans to initiate a Phase 1 study for RG-101 in 2014. Regulus is also developing RG-012, an anti-miR that targets microRNA-21 for the treatment of Alport Syndrome. Regulus currently plans to develop RG-012 to proof-of-concept. At that stage of development, Regulus' partner Sanofi has an exclusive option to license. We are eligible to receive a portion of all milestone payments Regulus receives from Sanofi if Sanofi chooses to exercise its option to license RG-012 from Regulus and RG-012 advances in development. We are also eligible to receive royalties on any future product sales of both of these drugs.

In October 2012, Regulus completed an IPO, in which we participated by purchasing $3 million of Regulus' common stock at the offering price. We remain a significant shareholder with approximately seven million shares. We began accounting for our investment in Regulus at fair value in the fourth quarter of 2012 when our ownership in Regulus dropped below 20 percent and we no longer had significant influence over Regulus' operating and financial policies. In the fourth quarter of 2012, we recorded an $18.4 million gain because of the increase in Regulus' valuation resulting from its IPO.

Regulus has successfully developed strategic partnerships with partners such as Sanofi, GSK, Biogen Idec and AstraZeneca. We benefit from Regulus' strategic partnerships because we have the potential to receive a portion of upfront payments, future milestone payments, and royalty payments. For example, under Regulus' strategic partnership with Sanofi, and as a result of our agreement with Regulus, we and Alnylam each received 7.5 percent, or $1.9 million, of the $25 million upfront payment and are eligible to receive 7.5 percent of all future milestone payments, in addition to royalties on any product sales. During 2013, 2012 and 2011, we did not earn any revenue from our relationship with Regulus.

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Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for anemia of chronic disorders, or ACD. 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. Because repayment of the promissory note was uncertain, we did not record any revenue from the upfront payment when we entered into the agreement. In May 2012, Xenon selected XEN701, a drug designed to inhibit the production of hepcidin, as a development candidate. In June 2013, we earned a $2 million license fee when Xenon exercised its option to an exclusive worldwide license to XEN701. In addition, in June 2013 Xenon repaid the $1.5 million convertible promissory note. We recognized the $2 million license fee and the $1.5 million upfront payment as revenue in the second quarter of 2013. In the first quarter of 2014, Xenon decided to discontinue development of XEN701. As a result, we will regain the rights to discover and develop antisense drugs to target hemojuvelin and hepcidin. During 2013, 2012 and 2011, we earned revenue of $3.5 million, $84,000 and $80,000, respectively, from our relationship with Xenon.

External Project Funding

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. In 2013, we made two payments to CHDI totaling $3 million associated with the progression of our Huntington's disease program, which we recorded as research and development expense. If we achieve pre-specified milestones under our collaboration with Roche, we will make additional payments to CHDI. During 2013, 2012 and 2011, we earned revenue of $414,000, $2.0 million and $2.4 million, respectively, from our relationship with CHDI. Our balance sheet at December 31, 2012 included deferred revenue of $229,000 related to our relationship with CHDI.

The Ludwig Institute; Center for Neurological Studies

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

Technology and Intellectual Property Sale and Licensing Agreements

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

Abbott Molecular Inc.

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

Under the stock purchase agreement, AMI will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, from the date of the acquisition closing through December 31, 2025. The earn out payments will equal five percent of Ibis' cumulative net sales over $140 million and up to $2.1 billion, and three percent of Ibis' cumulative net sales over $2.1 billion. AMI may reduce these earn out payments from five percent to as low as 2.5 percent and from three percent to as low as 1.5 percent, respectively, upon the occurrence of certain events. During 2013, 2012 and 2011, we did not earn any revenue from our relationship with AMI.

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

In December 2001, we licensed to Eyetech certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases. Pfizer Inc. markets Macugen outside of the United States and Valeant markets the drug in the United States. In February 2012, Eyetech was acquired by Valeant Pharmaceuticals International, Inc. Eyetech paid us a $2 million upfront fee and agreed to pay us for the achievement of pre-specified events and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in payments, and this license may also generate additional payments aggregating up to $2.8 million for the achievement of specified regulatory events with respect to the use of Macugen for each additional therapeutic indication. In 2013, 2012 and 2011, we earned $362,000, $499,000 and $790,000, respectively, of revenue related to royalties for Macugen under this license.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access

to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. In April 2011, we expanded our relationship with Roche Molecular Systems by granting Roche Molecular Systems a non-exclusive license to additional technology for research and diagnostic uses. During 2013, 2012 and 2011, we earned revenue of $618,000, $1.0 million and $828,000, respectively, from our relationship with Roche Molecular Systems. Our balance sheet at December 31, 2012 included deferred revenue of $400,000 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 small interfering RNA, or siRNA, therapeutics. Idera retained the right to practice its licensed antisense patent technologies and to sublicense its technologies to collaborators under certain circumstances. In addition, Idera received a non-exclusive license to our suite of ribonuclease H, or RNase H, patents. During 2013, 2012 and 2011, we earned revenue of $10,000 for each period from our relationship with Idera.

University of Massachusetts

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

Verva Pharmaceuticals Ltd.

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

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to ISIS-SMN$_{Rx}$. If we successfully develop and commercialize a drug incorporating the technology we licensed from the Cold Spring Harbor Laboratory, we will pay milestone payments to the Cold Spring Harbor Laboratory totaling up to $600,000 for the achievement of key clinical and regulatory milestones. In addition, we will pay the Cold Spring Harbor Laboratory a portion of any sublicense revenue we receive in consideration for sublicensing the Cold Spring Harbor Laboratory's technology and a royalty on sales of ISIS-SMN$_{Rx}$ if our product incorporates the technology we licensed from the Cold Spring Harbor Laboratory.

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8. Concentration of Business Risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10 percent or more of our total revenue, was as follows:

	2013	2012	2011
Partner A	25%	8%	0%
Partner B	24%	8%	18%
Partner C	22%	66%	73%
Partner D	20%	9%	0%

Contract receivables from three significant partners comprised approximately 91 percent of our contract receivables at December 31, 2013 and contract receivables from four significant partners comprised approximately 83 percent of our contract receivables at December 31, 2012.

9. Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($17,500 and $23,000 in 2013 for employees under 50 years old and employees 50 years old or over, respectively). We made approximately $574,000, $529,000 and $487,000 in matching contributions for the years ended December 31, 2013, 2012 and 2011, respectively.

10. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates. We do not believe, relative to our current legal proceedings, that a loss is

both probable and estimable. As such, as of December 31, 2013, we do not have a liability related to any of our current legal proceedings, including the following matters.

Santaris Litigation

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringes U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion, and the case is proceeding.

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Gilead Litigation

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

11. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2013 and 2012 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2013 Quarters				
Revenue	$ 43,360	$ 38,092	$ 23,585	$ 42,248
Operating expenses	41,735	46,020	49,090	62,106
Income (loss) from operations	1,625	(7,928)	(25,505)	(19,858)
Net loss	$ (1,672)	$ (10,126)	$ (24,570)	$ (24,276)
Basic and diluted net loss per share (1)	$ (0.02)	$ (0.09)	$ (0.21)	$ (0.21)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2012 Quarters				
Revenue	$ 23,235	$ 47,340	$ 11,601	$ 19,873
Operating expenses	41,690	43,644	39,647	45,992
Income (loss) from operations	(18,455)	3,696	(28,046)	(26,119)
Net loss	$ (23,995)	$ (1,207)	$ (37,639)	$ (2,637)
Basic and diluted net loss per share (1)	$ (0.24)	$ (0.01)	$ (0.37)	$ (0.03)

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

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076, 333-188407 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408) of Isis Pharmaceuticals, Inc. and in the related Prospectus of our reports dated February 28, 2014, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2013.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2014

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, 2014

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: February 28, 2014

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen

Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc. (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2013, 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, 2014

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	*Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request**.**

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.