2008
ANNUAL REPORT

Dear Fellow Shareholders,

2008 has been a year of great progress for Isis. Progress across every element of our business, and progress that is predicated on the investments and innovations we have made. The value we have created in Isis is built upon our leadership in antisense technology and our unique business model. Our value can be measured by the size of our intellectual property estate, our large pipeline of first-in-class drugs, the number and quality of our partnerships, and our strong financial position.

We pioneered antisense technology. We believe that antisense technology is improving the overall productivity of drug discovery and development to create better drugs for patients. Because of this belief, we have invested time, effort and money to build a robust and efficient drug discovery platform that supports the creation of a large pipeline of first-in-class drugs designed to offer significant therapeutic benefit to patients.

The productivity of antisense technology has allowed us to adopt a novel and successful business model. Our strategy is to invest in drug discovery and early development, and license our drugs at clinical proof-of-concept. This allows us to do what we do best without the need to build costly late-stage clinical programs, marketing or other kinds of commercialization infrastructure. We can maximize the return to our shareholders through license fees, milestone payments and royalties on drugs our partners are developing. By licensing our drugs after clinical proof-of-concept, we can create and nurture far more drugs, fueling a pipeline that is unparalleled in biotechnology and growing every year. This is the business model that we created at Isis. We feel that we are just beginning to realize the value of our model and its potential to provide us with long-term financial stability and success.

Our recent transactions have added more than $650 million in cash to Isis. We ended 2008 in the strongest cash position in the history of Isis, and we were profitable on a pro forma basis for the year. Furthermore, we will be profitable again in 2009. We have reported great success in the execution of our unique business strategy. Over the past two years, we have added Bristol-Myers Squibb (BMS), Ortho-McNeil Janssen Pharmaceuticals and Genzyme to our list of major pharmaceutical company partners. We have added a number of new satellite companies including Regulus, Altair and Excaliard. Each of these enterprises moves the technology and drugs forward and broadens the opportunities accessible to us and our shareholders. Moreover, we completed the sale of our diagnostic satellite company, Ibis, to Abbott.

This is the value proposition of antisense: antisense provides a direct route from genomics to drugs. Isis is the leader in this technology. We have demonstrated that antisense technology can dramatically improve the productivity of drug discovery and development by creating more drugs more rapidly. For example, in approximately two years from the publication of research identifying the gene function of PCSK9, we had initiated a research program targeting PCSK9, licensed the program to BMS and together with BMS selected a development candidate. This development candidate is now getting ready to enter clinical

development. This is the power of our technology. We can rapidly capitalize on insights in genomic information to make novel drugs, and we can do this over and over again. We can confidently say that we will add three to five new drugs to our pipeline each year. We can do all of this with fewer than 300 people in our research and development organization, which allows us to maintain an effective and relatively stable cost structure.

We also continue to expand the applications for our technology and strengthen our dominant intellectual property position, which provides us with significant control over oligonucleotide-based therapeutic approaches. We have over 1,600 issued patents and thousands of applications pending, and we continue to add to our vast patent estate, which not only protects our innovations, but also enables us to generate revenue by providing our partners multiple opportunities to participate in the success of our antisense technology. After years of perseverance, we believe we are realizing our aspirations for antisense technology.

In short, we can create new drugs each year and move them into the clinic, continue to play a leadership role in advancing antisense technology, continue to be one of the most innovative companies in the world on a per employee basis, all while maintaining a manageable cost structure.

We begin 2009 in a strong cash position and with a business strategy that will sustain our financial position. We plan to advance the drugs in our pipeline, to complete more comprehensive Phase 2 studies than we have been able to perform in the past, and to license our Phase 2 drugs on favorable financial terms. We plan to continue to grow our pipeline, while we continue to make advancements in our technology. In addition, we will continue to evaluate new opportunities that are not on our critical path, and, if appropriate, we will create new satellite companies or find other means to assure that they are aggressively pursued.

In 2009, of course, mipomersen will be center stage. We will complete the first Phase 3 study on mipomersen, advance the additional Phase 2 and Phase 3 studies, progress in our registration planning both in the US and Europe and complete the planning for the outcome study. But mipomersen is only part of the Isis story. In 2009, we expect progress across our entire pipeline, advances in our antisense technology and successes in our business.

Thank you for your ongoing support.

Stanley T. Crooke, M.D., Ph.D.

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, 2008

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

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

Common Stock, $.001 Par Value

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

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

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

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

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on the NASDAQ Global Market was $921,383,993 as of June 30, 2008.*

The number of shares of voting common stock outstanding as of February 19, 2009 was 97,595,098.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement for the fiscal year ended December 31, 2008 to be filed on or about April 6, 2009 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 2, 2009 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 63 to 66 incorporates several documents by reference as indicated therein.

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* Excludes 27,845,955 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, 2008. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

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

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

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

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

Vitravene® is a registered trademark of Novartis AG.

CORPORATE INFORMATION

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

PART I

Item 1. Business

Overview

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

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

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

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology because the clinical trials demonstrate that antisense drugs can work in man. With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform, increased the value of our drugs, and created renewed interest from potential partners in antisense technology.

In addition to mipomersen, many of the other drugs in our pipeline are demonstrating encouraging therapeutic activity in a variety of diseases. For example, our partner, OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc., reported Phase 2 data showing that an antisense drug provides survival advantage in patients with prostate cancer compared to standard therapies, and our partners Antisense Therapeutics Limited, or ATL, and Teva Pharmaceutical Industries Ltd., reported Phase 2 data demonstrating that an antisense drug can have a highly significant effect on disease activity in patients with multiple sclerosis, or MS, after only two months of treatment. These data highlight the broad therapeutic activity of antisense drugs and the power of our antisense technology platform to generate drugs that address significant medical needs.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Over the past two years, we established a number of notable pharmaceutical partnerships, which include partnerships with Genzyme, BMS and OMJP, to develop and commercialize many of our key cardiovascular and diabetes drugs. Our recent partnerships, including our strategic alliance with AMI, have generated an aggregate of more than $650 million in payments from licensing fees, equity purchase payments and milestone payments with the potential to earn over $2.5 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Beyond drug development, we create significant shareholder value through products of our inventions that other companies are developing and commercializing. For example, Ibis was a product of our innovative technology with applications in a number of areas, including infectious disease detection in hospital and clinical settings. In 2008, we entered a strategic alliance with AMI that ultimately resulted in AMI purchasing Ibis for a total purchase price of $215 million. We will continue to benefit from the success of Ibis through earn out payments from the sales of Ibis commercial products. This transaction represents a significant valuation for Ibis and a reflection of the value that we have built through our Ibis business.

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

Below is a list of some of our key accomplishments for 2008 and early 2009.

2008 and Early 2009 Business Highlights

Pipeline Highlights

We continued to expand our cardiovascular franchise with the addition of new drugs into development that enable us to broaden our therapeutic focus. Mipomersen, our flagship drug, matured appreciably during the last year. We and our partner Genzyme, are currently evaluating mipomersen in four Phase 3 studies with an NDA filing for the initial indication planned for the second half of 2010.

- We licensed mipomersen to Genzyme as part of a strategic alliance and together with Genzyme we made significant progress on our mipomersen project.
  - The transaction included a $175 million licensing fee, a $150 million equity investment at $30 per share, over $1.5 billion in potential commercial and developmental milestone payments for mipomersen, a share of profits for us on mipomersen ranging from 30 to 50 percent of commercial sales, and a preferred partner relationship for the development and commercialization of antisense drugs for central nervous system diseases and a number of rare diseases.
  - We completed enrollment of our Phase 3 mipomersen study in homozygous FH subjects and initiated four additional mipomersen studies, including three Phase 3 studies in heterozygous FH, high-risk high-cholesterol and severe high-cholesterol subjects and a Phase 2 study in high-risk, high-cholesterol subjects who are intolerant to statins.
  - We reported updated safety data on mipomersen from an ongoing open-label extension study that showed mipomersen continues to be well tolerated throughout longer-term treatment in FH patients who have been exposed to mipomersen from three to 23 months.
  - We reported data from a Phase 2 mipomersen liver imaging study in heterozygous FH subjects.
  - We reported two preclinical studies in which the lowering of apoB-100, resulted in the significant reduction of atherosclerotic plaques in murine models of atherosclerosis.
  - We received a patent that broadly covers the use of antisense compounds targeting apoB messenger RNA except a ribozyme. It is the first allowance in a series of broad filings protecting the therapeutic use of targeting apoB for the lowering of all atherogenic lipids, including LDL-C and triglycerides.
  - We published a preclinical study in *Circulation* showing that mipomersen lowers oxidized-LDL and Lp(a), a generally accepted independent risk factor for cardiovascular disease.

We continued to make progress in other programs in our cardiovascular franchise in which we believe there are significant opportunities for growth.

- We initiated a Phase 1 study of ISIS-CRP$_{Rx}$, an antisense drug that targets CRP.
- Together with BMS, we identified a development candidate that targets PCSK9 and received a $2 million milestone payment from BMS.
- We provided information on earlier preclinical programs including our antithrombotic program during the 2008 American Heart Association conference.

Our metabolic disease franchise continued to expand with new research efforts focused on attractive targets for the treatment of obesity.

- We initiated a Phase 1 study of ISIS-SGLT2$_{Rx}$, an antisense drug that targets SGLT2 for type 2 diabetes.
- We highlighted our robust diabetes and obesity portfolio with nine presentations and posters at the 2008 American Diabetes Association meeting. This included new preclinical data relating to ISIS-SGLT2$_{Rx}$ and results from eight research programs on novel targets that offer new mechanisms to address metabolic diseases, including obesity.

Cancer continues to be a disease in which antisense drugs could offer new treatment options to patients. We have begun to expand our internal focus on cancer and our partners are making excellent progress developing antisense drugs we have discovered to treat cancer.

- OncoGenex is evaluating OGX-011 in multiple Phase 2 studies in prostate, lung and breast cancer.

- OncoGenex has reported encouraging data on OGX-011, including recent Phase 2 data that showed OGX-011 provided an overall survival advantage when combined with standard first-line chemotherapy in prostate cancer patients compared to standard first-line chemotherapy alone.
- Previously reported data has shown better than expected survival when OGX-011 was combined with second-line chemotherapy as well as reduced levels of clusterin, OGX-011's target, and demonstrated durable reduction in pain and a decline in levels of PSA, a protein that is often elevated in patients with prostate cancer.
- OncoGenex reported survival data on OGX-011 from a Phase 1/2 study in patients with NSCLC. At two years, 30% of patients that had received OGX-011 with first-line chemotherapy were alive, comparing favorably to other previously reported studies in NSCLC.
- The FDA granted OGX-011 Fast Track Designation for use in combination with docetaxel for progressive metastatic prostate cancer.
- OncoGenex reached an agreement with the FDA on the design of a Phase 3 registration trial of OGX-011 in patients with castrate resistant prostate cancer, via the Special Protocol Assessment process.

- Lilly reported positive Phase 1 clinical trial results for LY2181308 that targets survivin for the treatment of cancer, and advanced LY2181308 into multiple Phase 2 trials.

In addition, many of our other partners are showing encouraging results with our antisense drugs in a broad range of diseases, including MS.

- ATL licensed ATL/TV1102, an antisense drug for patients with MS, to Teva.
  - ATL and Teva reported encouraging Phase 2 results for ATL/TV1102 at the World Congress on Treatment and Research in Multiple Sclerosis showing that ATL/TV1102 demonstrated a highly significant effect on disease activity in MS patients after only two months of dosing.
- Atlantic Pharmaceuticals Limited received U.S. orphan drug designation for alicaforsen for the treatment of pouchitis.
- Excaliard Pharmaceuticals, Inc. selected a development compound, EXC001, for the local treatment of fibrosis and scarring.
- iCo Therapeutics Inc. reported interim data from an ongoing Phase 1 study evaluating iCo-007 in patients with diffuse diabetic macular edema that showed iCo-007 appears to be well tolerated.
- Altair Therapeutics Inc. advanced AIR645 into Phase 1 studies. AIR645 is an antisense drug we discovered and licensed to Altair in 2007 to treat respiratory conditions.
- Achaogen initiated Phase 1 studies on Achaogen's neoglycoside, Achaogen's next-generation aminoglycoside drug, ACHN-490. ACHN-490 is being developed to treat bacterial infections and incorporates our aminoglycosides technology that we licensed to Achaogen. We received a $1 million milestone payment.

Corporate Highlights

Building upon our successes in 2007, we continued to improve our financial position in 2008, strengthening our balance sheet and bringing us closer to sustainable profitability driven by the successful execution of our business strategy.

- We exceeded our 2008 net operating loss guidance.
- We exceeded our 2008 cash guidance of $450 million and ended 2008 with over $490 million in cash.
- Our net loss applicable to common stock was $12.0 million, and if we exclude our non-cash stock compensation expense, we finished the year with net income.
- In early 2009, we added $175 million of cash to our balance sheet from the sale of our Ibis subsidiary.

We also added new patents to our intellectual property estate and expanded the scope of our core antisense patents.

- We were granted patents that significantly expand the scope of Isis' "Crooke" patent estate. U.S. Patent No. 7,432,250 and U.S. Patent No. 7,432,249 add broad claims that cover RNA-based product compositions and methods of treatment.

We recently sold our Ibis subsidiary to AMI. We believe the sale of Ibis to AMI will help ensure that Ibis is both technically and commercially successful as Ibis moves its technology into the clinical diagnostics market.

- AMI purchased Ibis for a total acquisition price of $215 million, and we will receive earn out payments tied to sales of Ibis systems, including instruments and assay kits.

Regulus Highlights

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development and commercialization of microRNA-based therapeutics.

- Regulus entered into a strategic alliance with GSK, which could provide up to nearly $600 million to Regulus, including a $20 million upfront payment. The alliance focuses on the development of microRNA-targeted therapeutics to treat inflammatory diseases.
- Regulus and academic collaborators continue to advance the basic understanding of microRNAs and the role that microRNAs play in disease. These advances were published in some of the industry's leading scientific journals, including Molecular and Cellular Biology, Cancer Cell and Nature.

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Development Projects

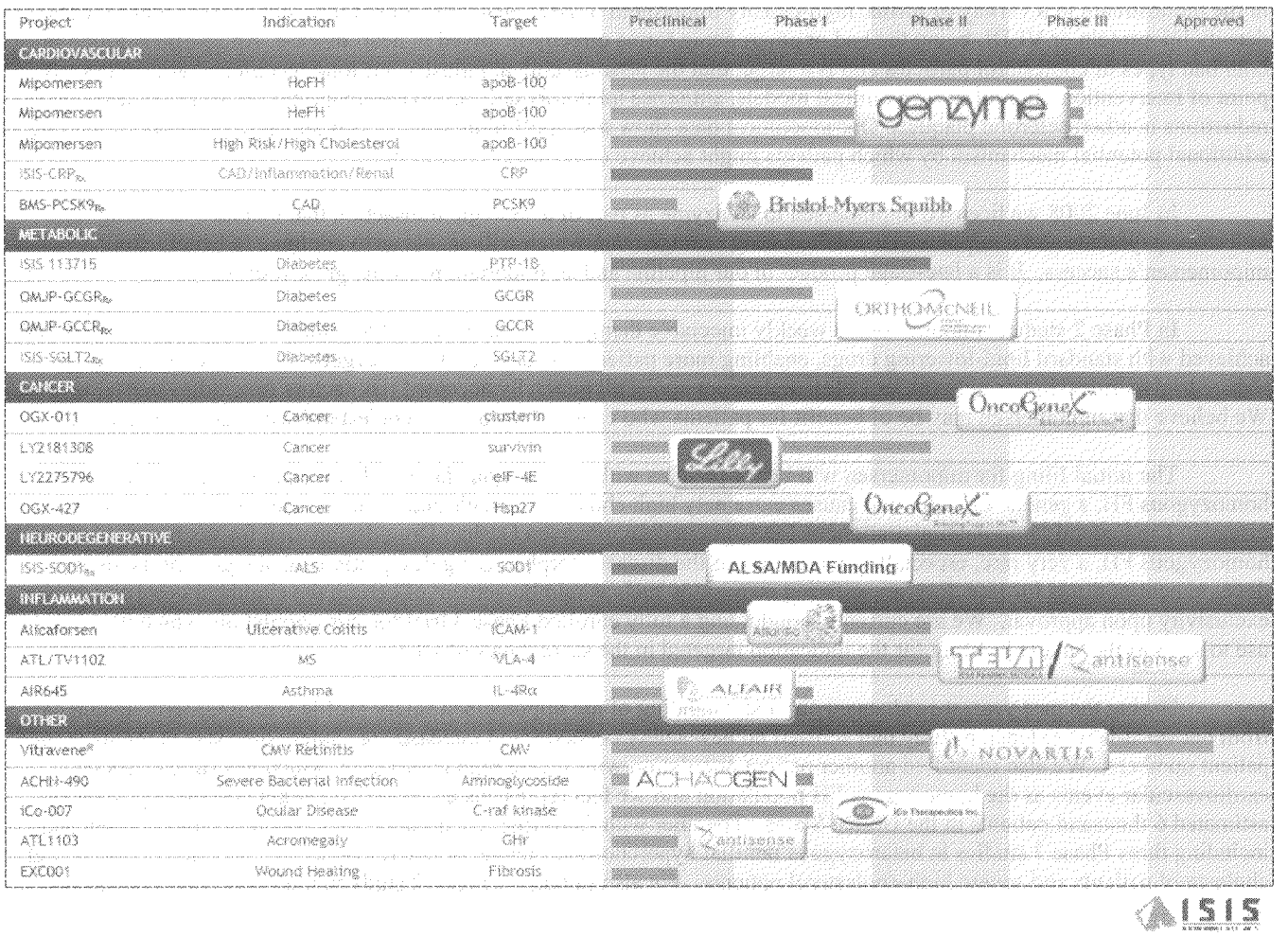
We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. With our proprietary drug discovery platform we can rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer.

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 great advances in chemistries, which we call our second-generation antisense drugs. Second-generation, including generation 2.2, antisense drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. Our scientists have utilized our chemistry advancements to expand the therapeutic and commercial opportunities of our pipeline. These advancements along with the shared manufacturing and analytical processes, shorten our timeline from initial concept to the first human dose.

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

The following table lists our approved product and each of our and our partners' drug development projects, their targets, disease indications and the development status of each. Prior to Phase 2 studies, we identify our drugs by the party responsible for development and the target, such as BMS-PCSK9$_{Rx}$ or ISIS-SGLT2$_{Rx}$, except when our partners refer to a drug by the partner's own compound number, such as AIR645 or EXC001. As our drugs advance in clinical development, we will adopt nonproprietary names given to each drug from the United States Adopted Names Council. For example, mipomersen is a nonproprietary name that we obtained for ISIS 301012 in 2007.

Pipeline



Cardiovascular Franchise

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

Mipomersen— Mipomersen is a first-in-class apo-B synthesis inhibitor currently in Phase 3 development. It is intended to reduce LDL-cholesterol, or LDL-C, by preventing the formation of atherogenic lipoproteins. We plan to develop mipomersen for patients who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. Lowering high cholesterol represents a large market opportunity, in which patients still need new treatment options. The current recommendations from the National Cholesterol Education Program's Adult Treatment Panel III are for LDL-C goals of less than 100 mg/dL for very high-risk patients and less than 130 mg/dL for moderately high-risk patients. The very high-risk population in the United States is about 1.5 to 2 million patients, who are either compliant on both statins and ezetimibe or who are highly statin intolerant.

Mipomersen's mechanism of action is to reduce the production of apolipoprotein B-100, or apoB-100, which is the protein that carries certain forms of cholesterol and triglyceride particles in the bloodstream. ApoB-100 can carry cholesterol in the bloodstream in a variety of forms, high-density lipoprotein or HDL being the good form, and LDL-C, and very low-density lipoprotein or VLDL being the bad or atherogenic forms directly involved in heart disease. ApoB-100 is found in both bad types of cholesterol particles and is a target that the pharmaceutical industry has long recognized as an attractive point of intervention. In multiple preclinical models, antisense inhibitors targeted to apolipoprotein B, or apoB, demonstrate reductions in atherosclerotic plaques. Our preclinical data show that apoB inhibition itself is anti-inflammatory, providing an additional potential mechanism by which patients might achieve cardiovascular benefit.

In June 2008 we licensed mipomersen to Genzyme as part of a strategic transaction that included licensing fees, milestone payments and a mipomersen profit sharing arrangement, which will enable us to continue to benefit from mipomersen's success. It is a late-stage product in our pipeline and an important potential growth-driver for us.

In Phase 2 studies, mipomersen, a weekly injectable therapeutic, was observed to reduce LDL-C beyond reductions achieved with standard lipid-lowering drugs, enabling more patients to achieve LDL-C targets. It was also observed to reduce triglycerides, lipoprotein (a), or Lp(a), and serum apoB, all generally accepted risk factors for cardiovascular disease. We believe that mipomersen may be of benefit for patients who cannot control their cholesterol with current therapies.

The initial filing for mipomersen will be for patients with homozygous familial hypercholesterolemia, or homozygous FH, a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease. The Federal Drug Administration, or FDA, granted mipomersen Orphan Drug designation for treating patients with homozygous FH, a very rare, especially severe form of the disease. Orphan Drug designation encourages and facilitates development of drugs for rare diseases, offering provisions such as reimbursement of certain development costs and market exclusivity upon approval. We are currently conducting a fully enrolled Phase 3 trial for this population, which we intend to use to support the first U.S. filing for the indication targeted in the second half of 2010.

During the past year, we enhanced our understanding of the mipomersen safety profile with long-term dosing data from our open-label extension study that showed no new safety concerns and increased our safety database in duration and patient numbers. We also identified another patient population with severe high cholesterol, which has similar risk of cardiovascular events as the homozygous FH population and we feel represents an attractive market opportunity, with an estimated 6 thousand patients in the United States. Together with Genzyme, we initiated four additional mipomersen studies, including three Phase 3 studies in heterozygous familial hypercholesterolemia, or heterozygous FH, patients, high-risk high-cholesterol patients and severe high-cholesterol patients. We also initiated a Phase 2 study in high-risk, high-cholesterol patients who are intolerant to statins.

These trials will provide additional data on mipomersen in high-risk patient populations and expand our experience with new patient populations, including patients with severe high cholesterol, statin intolerant patients and patients with type 2 diabetes. These studies will substantially increase the size of the database of patients treated with mipomersen, maximizing the profile and potential for the drug. We and Genzyme expect the data to help inform the design of a clinical outcomes study of mipomersen, potentially increasing the probability of success of that trial. The outcomes study may also support the eventual potential expansion of mipomersen's label to include a broader group of at-risk, high-cholesterol patients and we anticipate starting the outcomes study in mid 2010.

ISIS-CRP$_{Rx}$— ISIS-CRP$_{Rx}$, is a generation 2.2 antisense drug that inhibits CRP, a protein produced in the liver. CRP levels increase dramatically during inflammatory disorders, and excessive amounts of CRP have been linked to coronary artery disease. Furthermore, a growing body of evidence from clinical trials implicates CRP in cardiovascular disease progression. These results suggest that it may be therapeutically beneficial to significantly decrease CRP levels in patients who are at risk for coronary events. In addition, clinicians have associated elevated CRP levels with a worsening of overall outcomes in conditions such as end-stage renal disease, suggesting that lowering CRP could help these patients. CRP elevation is also evident in many other major inflammatory diseases such as Crohn's disease and rheumatoid arthritis.

In preclinical studies, we observed dramatic suppression of liver and serum CRP levels with our antisense inhibitor of CRP. ISIS-CRP$_{Rx}$ is currently in a Phase 1 blinded, randomized, placebo-controlled, dose-escalation study designed to assess the safety and pharmacokinetic profile of our drug in addition to the initial effects of our drug on baseline CRP levels in healthy volunteers. We plan to complete Phase 1 studies and finalize selection of disease indications for Phase 2 studies in 2009.

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

In May 2007, BMS entered into a collaboration with us to identify antisense drugs that target PCSK9. In 2008, we achieved the first milestone in this collaboration with the selection of BMS-PCSK9$_{Rx}$ as a development candidate. BMS-PCSK9$_{Rx}$ could offer a new and complementary mechanism to current lipid-lowering therapies for the prevention and treatment of cardiovascular diseases. BMS intends to initiate Phase 1 studies on BMS-PCSK9$_{Rx}$ in 2009.

Cardiovascular research—We continue to build our cardiovascular disease franchise by evaluating potential drug targets that influence the onset and progression of cardiovascular disease. In addition, we intend to expand our cardiovascular franchise with additional drugs to treat various aspects of cardiovascular disease through complimentary mechanisms. For instance, studies have shown that humans with increased levels of Factor XI are at an increased risk for blood clots forming in their veins, heart attacks and potential strokes. Clotting factors, including Factor XI, are areas of active research for us and could lead to the development of potent and highly effective drugs to treat disease. Using antisense compounds we inhibited all of the clotting factors that are made in the liver, and we are evaluating each clotting factor as a potential antisense drug target. In November 2008, we presented a cardiovascular review during the annual meeting of the American Heart Association in which we provided additional detail on our Factor XI program and other late-stage research programs. And finally, we continue to add to our scientific understanding of our drugs and other disease targets, including the biological processes that are linked to our disease targets and the impact of our drugs on these processes.

Metabolic Franchise

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

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

Scientists have long recognized PTP-1B as an attractive target for treatment of diabetes, but due to structural similarities among closely related proteins, pharmaceutical companies have had difficulty identifying small molecule drugs with sufficient specificity to be safe. Our antisense technology allows us to design very specific drugs that inhibit PTP-1B and that do not inhibit other protein family members, making it possible to reduce PTP-1B activity without affecting other closely related proteins that would likely lead to unwanted side effects.

ISIS 113715 is currently in Phase 2 development for the treatment of type 2 diabetes. In humans and preclinical studies, ISIS 113715 has demonstrated reductions in blood glucose without causing low blood sugar, weight gain or nausea. As part of our Phase 2 program, we are conducting a combination study of ISIS 113715 in patients with type 2 diabetes. Because our initial registration plan for ISIS 113715 is as an adjunct to insulin therapy, we are evaluating it in combination with sulfonylureas. Sulfonylureas, which are commonly prescribed oral antidiabetic drugs, increase insulin secretion in the body and therefore they offer the best approximation of a combination with insulin therapy in the milder disease setting appropriate for this first combination experience with ISIS 113715. We plan to report Phase 2 data on ISIS 113715 during 2009.

OMJP-GCGR —We licensed our glucagon receptor, or GCGR, program to OMJP as part of a metabolic disease collaboration we established in 2007. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, should lower blood glucose and help control type 2 diabetes.

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

We and our partner, OMJP, completed a Phase 1 study on OMJP-GCGR$_{Rx}$ that we designed to assess activity and safety in healthy volunteers. We are working with OMJP to determine the future development plan for our GCGR program.

OMJP-GCCR —We licensed our glucocorticoid receptor, or GCCR, program to OMJP as part of a metabolic disease collaboration we established in 2007. Glucocorticoid hormones have a variety of effects throughout the body, including promoting liver glucose production and fat storage. Although scientists have long recognized the inhibition of GCCR as an attractive strategy for development of therapeutics for type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged developers of traditional drugs. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to antagonize glucocortocoid action primarily in liver and fat tissue. Notably, antisense drugs do not reduce GCCR expression in the central nervous system or adrenal glands. Inhibiting GCCR expression in these two organs can lead to systemic side effects.

In preclinical studies, we have shown that antisense inhibition of GCCR reduced levels of blood glucose, demonstrated a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and reduced body fat. These observations suggest that an antisense drug that inhibits GCCR could have a broad therapeutic profile. Together with our partner OMJP, we continue to progress the program.

ISIS-SGLT2$_{Rx}$— ISIS-SGLT2$_{Rx}$ is a generation 2.2 antisense drug targeting sodium—glucose co-transporter type 2, or SGLT2, which is the major transporter for blood sugar re-absorption in the kidney. By specifically blocking the production of SGLT2 in the kidney tissue, we can promote blood sugar excretion and reduce blood sugar levels, without having any effect on a related gene product, SGLT1.

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

We are evaluating ISIS-SGLT2$_{Rx}$ in a Phase 1 study designed to assess the safety and activity of the drug in healthy volunteers by measuring the effect on glucose excretion in urine. We expect to complete this Phase 1 study in normal volunteers in 2009.

Metabolic disease research—We now have four drugs in our pipeline to treat type 2 diabetes, each of which acts upon targets in the liver, fat tissue, or the kidney through distinct mechanisms to improve insulin sensitivity, reduce glucose production, or affect other metabolic aspects of this complex disease. We plan to continue to discover and develop antisense drugs to treat metabolic disease. For example, through our OMJP collaboration, we are working to identify additional antisense drugs to treat metabolic diseases. Additionally, we are expanding our research focus to obesity. In 2008 at the American Diabetes Association annual conference we presented data on eight research programs with novel targets that could offer new mechanisms to treat metabolic disease, including obesity. We feel that this is an area where antisense drugs can have an impact and as a result, we are actively evaluating many exciting obesity targets.

Cancer Portfolio

We are pursuing the discovery and development of antisense drugs to treat cancers internally and through our partnerships with OncoGenex and Lilly. Our current portfolio consists of four antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. We believe that our second-generation antisense drugs have properties that make them attractive therapies for cancer.

OGX-011— OGX-011 is a second-generation antisense inhibitor of clusterin, a secreted protein that acts as a cell-survival protein and is over-expressed in response to anti-cancer agents, like chemotherapy, hormone ablation and radiation therapy. We and OncoGenex jointly discovered and conducted the initial development of OGX-011. OncoGenex is now developing OGX-011 on its own.

OncoGenex recently reported positive survival results from a Phase 2 study of OGX-011 in combination with docetaxel and prednisone compared to docetaxel and prednisone alone for first-line treatment of metastatic castrate resistant prostate cancer. The National Cancer Institute of Canada, Clinical Trials Group conducted the trial and analyzed the data, which showed a median survival of 27.5 months compared to docetaxel and prednisone alone of 16.9 months in 82 patients with metastatic or locally recurring prostate cancer refractory to hormone therapy. The current results were based on study data with a median follow-up of approximately 30 months for both the OGX-011 and control arms. Results currently indicate that patients in the OGX-011 arm have a death rate of approximately 40% lower than patients in the control arm. The current 10.6 month median overall survival advantage observed in the OGX-011 group represents an increase over the median survival observed in the control group. As a basis for comparison, the FDA approved docetaxel based on a survival advantage of approximately 2.4 months over mitoxantrone.

Previous results regarding the primary endpoint analysis, PSA response, for this trial were presented at the American Society of Clinical Oncology 2007 annual meeting. In a Phase 2 study evaluating OGX-011 in combination with second-line chemotherapy for metastatic castrate resistant prostate cancer, OGX-011 showed better than expected survival results in combination with second-line chemotherapy, reduction in levels of serum clusterin, durable reductions in pain, and a decline in prostate specific antigen, or PSA, a protein that is often elevated in patients with prostate cancer.

In August 2008, the FDA granted OGX-011 Fast Track Designation as a treatment in combination with docetaxel for progressive metastatic prostate cancer. The FDA also agreed upon the design of a Phase 3 registration trial of OGX-011 with overall survival as the primary endpoint in patients with castrate resistant prostate cancer, through the Special Protocol Assessment process. In October 2008, the FDA confirmed the appropriateness of durable pain palliation as a primary endpoint for a second Phase 3 trial design for the product market approval for OGX-011 as a treatment for castrate resistant prostate cancer.

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

OncoGenex is currently evaluating OGX-011 in multiple Phase 2 clinical studies in prostate, lung and breast cancer. OncoGenex plans to initiate a Phase 3 study on OGX-011 in patients with prostate cancer, subject to availability of capital.

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

In single-agent preclinical studies, OGX-427 demonstrated significant anti-tumor activity at low concentrations. In addition, when combined with chemotherapy in preclinical prostate cancer studies, OGX-427 was able to significantly enhance the anti-tumor activity of the widely used chemotherapy drugs, such as docetaxel. OncoGenex is currently conducting a Phase 1 clinical study of OGX-427 in patients with breast, ovarian, bladder, prostate, lung cancer or NSCLC who have failed potentially curative treatments or for which a curative treatment does not exist. OncoGenex expects to complete this Phase 1 study of OGX-427 in 2009.

LY2181308—We licensed our anti-cancer drug, LY2181308, to Lilly as part of the companies' antisense drug discovery research collaboration in cancer. This drug targets survivin, which plays a role in cancer cell death and is one of the most commonly over expressed proteins in cancers. Our researchers and collaborators have shown that inhibiting the expression of survivin by LY2181308 inhibits the growth of cancer cells. Since normal cells in the body do not express survivin, we expect that this drug will have fewer side effects than traditional chemotherapy. Lilly recently completed its Phase 1 study of LY2181308 and presented first-in-human data from this study showing that the drug distributed to tumor cells with evidence of reduced survivin levels. Last year Lilly initiated two separate Phase 2 clinical studies examining LY2181308's effectiveness in patients with relapsed or refractory acute myeloid leukemia and as a combination therapy with docetaxel for treating hormone refractory prostate cancer. Lilly continues to progress in Phase 2 studies of LY2181308 in patients with a variety of cancers.

LY2275796—LY2275796 is the second antisense anti-cancer drug we have licensed to Lilly and is currently in Phase 1 development. This drug targets eukaryotic initiation factor-4E, or eIF-4E, a protein involved in tumor progression, angiogenesis and metastases, including breast, head and neck, prostate, lung, bladder, colon, thyroid and non-Hodgkin's lymphomas. In conjunction with scientists from Lilly and the Wood Hudson Cancer Research Laboratory, we published experimental data in The Journal of Clinical Investigation that suggests eIF-4E may act as a critical "switch" in cancer progression.

Neurodegenerative

We are pursuing the discovery and development of antisense drugs for neurodegenerative diseases in which there is a large unmet need for new treatment options. We have initiated several programs to develop drugs to treat severe neurodegenerative diseases, and have funded three of these programs through grants. Our most advanced of the programs, ISIS-SOD1$_{Rx}$ to treat amyotrophic lateral sclerosis, or ALS, also known as Lou Gehrig's disease, is currently in preclinical toxicology studies. In addition, as part of our alliance with Genzyme, we have a preferred partner relationship for the development and commercialization of antisense drugs for neurodegenerative and certain rare diseases.

ISIS-SOD1 $_{Rx}$—ISIS-SOD1$_{Rx}$ is our first drug to enter development that targets superoxide dismutase, or SOD1, a molecule associated with an inherited, aggressive form of ALS. The FDA granted ISIS-SOD1$_{Rx}$ Orphan Drug designation for the treatment of ALS. A small pump administers the drug directly into the central nervous system infusing the drug into the cerebral spinal fluid. Clinicians call this type of administration intrathecal infusion.

Researchers reported in the Journal of Clinical Investigation that treatment with ISIS-SOD1$_{Rx}$ prolonged life in rats that showed many symptoms of ALS. By delivering our drug directly to the fluid that circulates within the central nervous system, investigators were able to lower production of the mutant protein in neurons and surrounding cells. The ALS Association and the Muscular Dystrophy Association are providing funding for investigational new drug-enabling, or IND-enabling, studies for ISIS-SOD1$_{Rx}$. Additionally, as part of our alliance with Genzyme, Genzyme has the first right of refusal to license ISIS-SOD1$_{Rx}$ from us. We plan to initiate a Phase 1 clinical study on ISIS-SOD1$_{Rx}$ in patients with ALS in 2009.

Other Drug Development Highlights

The broad applicability of our antisense technology allows us to create promising drugs in a variety of disease areas, many of which are underserved with current treatment options. For instance, our partners ATL and Teva recently presented encouraging Phase 2 data on ATL/TV 1102 showing that ATL/TV 1102 significantly reduced disease activity in patients with MS. This data demonstrates the effectiveness of our antisense technology and represents promise for patients with MS. We have been successful in developing novel drugs and licensing them to highly focused satellite companies that have the specific expertise and resources to continue developing these drugs. Together with our partners we continue to advance new drugs into development and move antisense drugs into clinical studies that are outside of our core therapeutic areas.

ACHN-490—ACHN-490 is a neoglycoside, which is Achaogen's next-generation aminoglycoside drug that Achaogen is developing for the treatment of multi-drug resistant gram-negative bacterial infections. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. Achaogen developed ACHN-490, which incorporates aminoglycoside technology that we licensed to Achaogen. ACHN-490 has been observed to display broad-spectrum activity against multi-drug-resistant gram-negative bacteria that cause systemic infections, including E. coli and methicillin-resistant staphylococcus aureus. In preclinical studies, ACHN-490 demonstrated an acceptable safety profile and the potential for once-daily dosing.

AIR645—We have licensed AIR645 to Altair, a venture capital funded biotechnology company focused on the discovery, development and commercialization of our antisense drugs to treat respiratory conditions. AIR645 is an inhaled second generation antisense inhibitor of the alpha subunit of the interleukin 4 receptor, or IL-4R-alpha, which inhibits interleukin 4, or IL-4, and interleukin 13, or IL-13, signaling. IL-4 and IL-13 are two important cytokines in asthma, which regulate inflammation, mucus overproduction and airway hyper-responsiveness. In preclinical studies, we showed that inhibiting IL-4R-alpha with an antisense compound potently reduced target RNA and protein levels. Inhibiting IL-4R also demonstrated pharmacologic activity in mouse models of asthma that included reducing lung cytokine production, inflammation, and airway hyper-responsiveness. In addition, these studies showed that, when delivered by inhalation, AIR645 rapidly distributed to the airways and achieved therapeutic drug concentrations in multiple cell types with little systemic exposure. AIR645 is currently completing a Phase 1 study in normal volunteers and a Phase 1b study in asthmatic patients, and Altair plans to report the results of these studies in 2009. If the data are positive, Altair plans to begin Phase 2 studies in 2009.

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

ATL/TV1102—Now under license to Teva, ATL/TV1102 is an antisense inhibitor of CD49d, which is a subunit of Very Late Antigen-4, or VLA-4. Studies in animal models have demonstrated that inhibiting VLA-4 positively affects a number of inflammatory diseases, including MS.

We licensed ATL/TV1102 to ATL in December 2001 and, in February 2008, ATL licensed ATL/TV1102 to Teva, which has responsibility for continued development of ATL/TV1102. In 2008, Teva and ATL reported Phase 2a results of ATL/TV1102 showing significantly reduced disease activity in patients with relapsing remitting MS, for which we earned a milestone payment. Teva is completing additional preclinical studies to support long-term dosing in patients with MS, prior to continuing to a Phase 3 study.

ATL1103—ATL1103 is an antisense drug that inhibits growth hormone receptor, or GHr, which is a receptor that reduces the level of circulating insulin-like growth factor-1, or IGF-1, produced in the liver. IGF-1 is a hormone that contributes to various diseases including acromegaly, which is characterized by abnormal growth of organs, face, hands and feet, as well as for diabetic retinopathy, a common disease of the eye and a leading cause of blindness. In preclinical studies, ATL1103 demonstrated significant reductions in IGF-1 levels in the blood. ATL is currently evaluating ATL1103 in preclinical toxicity studies. ATL plans to complete IND-enabling studies for ATL1103 in 2009.

EXC001—EXC001 is a drug we discovered and licensed to Excaliard for the local treatment of fibrotic diseases, including scarring. Fibrosis represents a significant and expanding area of unmet medical need where antisense drugs could offer a unique advantage for anti-fibrotic agents. Excaliard expects to complete IND-enabling studies on EXC001 in 2009.

iCo-007—iCo-007 is an antisense inhibitor of c-Raf kinase. In preclinical studies, antisense inhibition of c-Raf kinase was associated with a reduction in the formation and leakage of new blood vessels in the eye, suggesting inhibiting c-Raf kinase can improve treatment for both diabetic macular edema and diabetic retinopathy. Diabetic retinopathy is one of the leading causes of blindness in people in the U.S., and nearly 100% of type 1 diabetics by age 20 have evidence of retinopathy. Additionally up to 21% of people with type 2 diabetes have retinopathy when they are first diagnosed with diabetes, and most will eventually develop some degree of retinopathy. We discovered iCo-007 and licensed it to iCo Therapeutics for the treatment of various eye diseases that occur as complications of diabetes. In 2008, iCo provided interim results of an ongoing Phase 1 study of iCo-007 in patients with diffuse diabetic macular edema. iCo intends to complete the Phase 1 study and report initial data in patients with diffuse diabetic macular edema treated with iCo-007 in 2009.

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

Antisense Technology

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

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

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

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

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

Other Antisense Mechanisms

RNAi

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

RNAi is an antisense mechanism that involves using small interfering RNA, or siRNA, as a method to target a mRNA sequence. With siRNA, the cell utilizes a protein complex called RNA-induced silencing complex, or RISC, to bind

to the mRNA and to prevent the production of a disease-causing protein. We have a strong and growing intellectual property position in RNAi methodology and oligonucleotide chemistry for siRNA therapeutics, and we have licensed these patents to Alnylam for double-stranded siRNA therapeutics, as part of our collaboration with them.

We are also developing technology for creating single-stranded drugs that work through the RNAi pathway, which we reserved the right to do under our license to Alnylam. At present, the double-stranded siRNA drugs in development are administered locally, or, to achieve sufficient systemic delivery, require special chemical formulation of the oligonucleotides. In contrast, our single-stranded second generation antisense drugs readily distribute to target organs including liver and kidney, and we are evaluating the feasibility of developing similarly well-behaved single-stranded RNA-like oligonucleotide drugs that act through the RNAi mechanism.

Splicing

Splicing is a cellular mechanism through which a single gene can lead to the production of many different, albeit closely related, proteins. To be converted into proteins, genes must be initially copied into a pre-mRNA. Pre-mRNA often contains extra sequence information that must be removed prior to translation into the protein. Scientists call this process splicing. Controlling pre-mRNA splicing can affect the production of proteins providing us with another way to control the production of disease-causing proteins. Using antisense technology, we have been able to control how these stretches of RNA are spliced back together. Our scientists in collaboration with Cold Spring Harbor recently published research that demonstrated the feasibility of using our antisense technology to control pre-mRNA splicing for the treatment of spinal muscular atrophy. This collaborative work demonstrates the diversity of our technology and the potential to utilize many different antisense approaches to treat disease.

New Antisense Targets

MicroRNAs

There are many different types of RNA that exist within the body, including pre-mRNAs and mRNAs. Our antisense technology is not limited to RNA sequences that translate into proteins, but rather we can apply the principals of our technology to develop drugs that target other RNAs, such as microRNAs. MicroRNAs are small, non-coding RNA molecules that work as natural antisense sequences that scientists believe regulate the expression of approximately one-third of all human genes. To date, scientists have identified more than 700 microRNAs in the human genome, and have shown that the absence or presence of specific microRNAs in various cells are associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. MicroRNAs themselves may be drug targets. For instance, if a single microRNA can change the expression of a protein that may be involved in disease, then inhibition of this microRNA could provide a therapeutic benefit. Alternately, microRNAs could be used as drugs themselves, where increasing the cell concentration of a particular microRNA could modulate the expression of a particular protein. To fully exploit the therapeutic opportunities of targeting microRNAs, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-based therapeutics.

Other Oligonucleotide Opportunities

Scientists can also design oligonucleotide molecules to directly target and bind to proteins to treat diseases. Aptamers are oligonucleotide molecules that form a three-dimensional shape that enables the aptamer to specifically bind to a protein molecule of interest for disease treatment. Aptamers differ from antisense inhibitors because they do not bind to an RNA sequence to inhibit protein formation, but rather they modify the function of a protein by binding directly to the protein. However, our patented chemical toolbox can greatly improve the chance that an aptamer will succeed as a drug. In 2007, we entered into a collaboration with Archemix to leverage aspects of our oligonucleotide chemistries, including manufacturing, for the development of aptamer drugs. As part of the agreement, Archemix gained access to part of our significant intellectual property estate relating to oligonucleotide chemical modifications in exchange for equity, milestone payments and royalties on aptamer drugs Archemix develops.

Regulus Therapeutics

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics. In addition, Regulus has assembled a strong leadership team with corporate management, business and scientific expertise, a board of directors that

includes industry leaders in drug discovery and development, and a scientific advisory board that consists of world-class scientists including some of the foremost authorities in the field of microRNA research.

Regulus Business

We and Alnylam granted Regulus exclusive licenses to our intellectual property for microRNA therapeutic applications, and Alnylam made an initial investment in Regulus of $10 million in 2007 to balance venture ownership. Thereafter, we and Alnylam share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

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

Regulus exclusively controls many of the early fundamental patent portfolios in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Our "Crooke" patent estate provides Regulus exclusive rights to RNA-based product compositions and methods of treatment in the field of microRNA-based therapeutics. Regulus has also continued to build upon its intellectual property estate through the exclusive license of intellectual property relating to antagonizing a specific microRNA, miR-181a, to regulate immune responses. In total, Regulus' intellectual property portfolio includes early fundamental intellectual property in the field of microRNA, as well as over 900 filed patent applications pertaining to chemical modification of oligonucleotides for therapeutic applications, of which over 600 have been issued.

In April 2008, Regulus formed a strategic alliance with GlaxoSmithKline, or GSK to discover, develop and market microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The transaction included a $20 million upfront payment to Regulus and up to $144.5 million in potential development, regulatory and sales milestone payments by GSK for each of the four microRNA-targeted therapeutics discovered as part of the collaboration. In total, the transaction has a potential value of nearly $600 million. Additionally, Regulus is eligible to receive royalties up to double digits on worldwide sales of products resulting from the collaboration.

Regulus Therapeutic Programs

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

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

Most recently, Regulus and its collaborators demonstrated that microRNA-targeted agents provided therapeutic benefit in an animal model of heart failure. This research supports the strategy of developing microRNA-based drugs to treat disease and provides the foundation for future research into the therapeutic benefit of microRNA-targeting for the treatment of heart failure. miR-122 is Regulus' most advanced program and Regulus is currently evaluating it for the treatment of HCV infection. The liver produces miR-122, which is a host gene the hepatitis C virus requires for viral infection.

Regulus' other therapeutic areas of focus include oncology, immunology and inflammation. As part of Regulus' alliance with GSK, Regulus has a research program in inflammation, where GSK has an exclusive option to license drugs developed from the program.

Ibis Biosciences, Inc.

In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total acquisition price of $215 million. The Ibis technology is a product of our innovation and a tangible example of the value our technology provides outside of drug discovery and development. In late 2007, we began commercializing the Ibis T5000 instrument and research kits used with the Ibis T5000. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in

expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. Early this year AMI completed the acquisition of Ibis and we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis systems that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5% of net sales over $140 million through net sales of $2.1 billion and 3% of net sales over $2.1 billion, with the percentages subject to reduction in certain circumstances. As a result, we believe this is a very attractive transaction for our shareholders.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a clinical development pipeline of 19 drugs, to create a broad base of potential milestones, royalties, profit sharing and earn out payments and to control our drug development expenses. In this way, we remain a focused and efficient research and development organization that can continue to discover new drugs and expand ours and our partners' pipelines. In order to maximize the value of our antisense technology and our drug discovery platform, we pursue several different categories of partnerships, including traditional pharmaceutical alliances and licenses, drug discovery and development satellite companies and technology development satellite companies. Our partnership strategy allows us to minimize our risk in discovering antisense drugs in new and underserved disease areas.

We concentrate on developing antisense drugs in our core focus areas, cardiovascular, metabolic and neurodegenerative diseases and cancer. These are disease areas in which there are large market opportunities and we can quickly obtain clinical proof of concept. We license drugs from our core therapeutic franchises to traditional pharmaceutical partners prior to the start of large Phase 3 programs and at other points during drug development that will provide the maximum value for our drugs.

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

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

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

Traditional Pharmaceutical Alliances and Licensing

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

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a research relationship. The transaction, which closed in June 2008, included a $175 million licensing fee, a $150 million equity investment in us where we issued Genzyme five million shares of our common stock at $30 per share, over $1.5 billion in potential milestone payments and a share of profits on mipomersen and follow-on drugs ranging from 30 to 50% of all commercial sales. Under this alliance, Genzyme is responsible for the commercialization of mipomersen. We will

contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme is our preferred partner for the development and commercialization of antisense drugs for neurodegenerative and certain rare diseases.

Genzyme has agreed that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen License and Co-Development Agreement, the first commercial sale of mipomersen or the termination of our mipomersen License and Co-Development Agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen License and Co-Development Agreement or the date Genzyme holds less than 2% of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

During 2008, we recognized revenue of $48.2 million related to the upfront payments we received from Genzyme, which represented 45% of our total revenue for 2008.

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

In September 2007, we entered into a collaboration with OMJP to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs. Additionally, OMJP is providing funding to us to support a focused research program in metabolic disease. Under the terms of the agreement, OMJP paid us a $45 million upfront licensing fee and is also providing us with research and development funding over the two year period of the collaboration. In addition to the licensing fee, we will also receive over $225 million in milestone payments upon successful development and regulatory approvals of antisense drugs that target GCGR and GCCR, as well as royalties on sales. We will also receive milestone payments and royalties on the successful development and regulatory approvals of additional drugs discovered as part of the collaboration.

In September 2007, we initiated the Phase 1 clinical trial in our OMJP-GCGR program for which we earned the first development milestone payment of $5 million. During 2008 and 2007, we recognized revenue of $31.9 million and $13.2 million, respectively, related to the upfront licensing fee, the milestone payment and the research and development funding, which represented 30% and 23% of our total revenue for those years.

Bristol-Myers Squibb Company

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

Pfizer Inc.

In May 2005, we entered into a multi-year drug discovery collaboration with Pfizer to identify second-generation antisense drugs for the treatment of ophthalmic disease. In addition to the collaboration agreement, we have entered into a target validation agreement with Pfizer. Under the terms of the collaboration agreement, we received an upfront technology access fee of $1 million. As of December 31, 2008, we earned milestone payments totaling $1.2 million under the collaboration agreement. In 2008, this collaboration ended in accordance with its terms. During 2008, 2007 and 2006, we earned revenue of $360,000, $445,000 and $547,000, respectively.

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly, which included a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases. Subsequently, we extended the research collaboration with Lilly to focus on a select number of targets. As part of the collaboration, Lilly licensed LY2181308, our

antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. As of December 31, 2008, we had earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. Lilly is responsible for the preclinical and clinical development of LY2181308 and LY2275796. We will receive additional milestone payments aggregating up to $25 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and in addition, royalties on future product sales of these drugs.

During 2008, we earned revenue from our relationship with Lilly totaling $156,000, compared to $402,000 and $1.2 million in 2007 and 2006, respectively.

Merck & Co., Inc.

In June 1998, we entered into a multi-year research collaboration and license agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a drug discovered in this collaboration into Phase 1 clinical trials for which we received a $1 million milestone payment. In addition to the milestone payment we received, Merck will pay us aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales. We recently removed the Merck drug from our pipeline because we have been unable to verify the development status of the drug with Merck. During 2008 and 2007, we did not recognize any revenue from our relationship with Merck, compared to $1.1 million in 2006, which was made up of the $1 million milestone payment and $60,000 pursuant to a non-exclusive license agreement.

Drug Discovery and Development Satellite Company Collaborations

Through our drug discovery and development satellite company collaborations, we continue to expand the reach and potential of RNA-based therapeutics into disease areas that are outside of our core focus areas. In addition, by capitalizing on our partners' resources and expertise, these partnerships allow more of our drugs to move forward in development than we could advance on our own. Further, these relationships provide us with partners who are focused in a particular disease area and who share the common goal of advancing our drugs. In these partnerships, we typically own equity in the company, often as part of the licensing agreement and we also retain the potential to earn milestone payments and royalties. We refer to these companies as our drug discovery and development satellite companies, and this strategy as our satellite company strategy. Our satellite company strategy allows us to create and support a much broader product pipeline than we could develop on our own.

Achaogen, Inc.

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

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a venture capital-funded biotechnology company focusing on the discovery, development and commercialization of our antisense drugs to treat asthma and other respiratory conditions. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an inhaled inhibitor of the IL-4 and IL-13 signaling pathways for the treatment of asthma. Altair is solely responsible for the continued development of AIR645. At December 31, 2008 and 2007, we owned 18% of Altair in the form of preferred stock. In addition to the preferred stock, we will receive additional license fees and royalties if AIR645 and other drugs arising out of the research collaboration progress. During 2008 and 2007, we recognized revenue of $207,000 and $494,000, respectively, from our relationship with Altair, which does not include any revenue from the equity we received from Altair.

Antisense Therapeutics Limited

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

In addition to ATL/TV1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we extended for an additional two years in January 2007. ATL pays us cash for access to our antisense expertise and for research and manufacturing services we may provide to ATL during the collaboration. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership.

During 2008, we recorded revenue of $1.6 million related to this collaboration compared to $80,000 and $652,000 for 2007 and 2006, respectively. At December 31, 2008 and 2007, we owned less than 10% of ATL's equity.

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based company that gastrointestinal drug developers founded in 2006 to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Pharmaceuticals plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. At December 31, 2008 and 2007, we owned approximately 13% of Atlantic Pharmaceuticals' equity. In addition, assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Pharmaceuticals meets specific development milestones, at Atlantic Pharmaceuticals' request, we will attempt to identify a second-generation lead drug candidate for Atlantic Pharmaceuticals. Atlantic Pharmaceuticals may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen, and, if selected, the second-generation lead drug candidate. During 2008 and 2007, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals because we do not recognize revenue when we receive equity in private companies.

Excaliard Pharmaceuticals, Inc.

In November 2007, we entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring. We have granted Excaliard an exclusive worldwide license for the development and commercialization of certain antisense drugs. Excaliard made an upfront payment to us in the form of equity and paid us $1 million in cash for the licensing of a particular gene target. At December 31, 2008 and 2007, we owned less than 10% of Excaliard's equity and we have no remaining performance obligations. In addition, assuming Excaliard successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $8.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs Excaliard develops, as well as a portion of the fees Excaliard receives if it licenses the drugs. During 2008 and 2007, we recognized revenue of $384,000 and $1 million, respectively, which does not include any revenue from the equity we received from Excaliard.

iCo Therapeutics Inc.

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

Over the course of our relationship with iCo they have paid us in a combination of cash and equity instruments, which included common stock and convertible notes. As a result of the equity instruments we received, on December 31, 2008, we owned less than 10% of iCo's equity, compared to approximately 10% at December 31, 2007. In February 2009, iCo completed a CAD$ 1.3 million financing to fund the completion of its Phase 1 clinical study of iCo-007. We participated in the financing and as a result our ownership in iCo is now approximately 14%. During 2008, we recognized revenue of $7,000 from our relationship with iCo, compared to $550,000 for 2006. During 2007, we did not recognize any revenue from our relationship with iCo.

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement with OncoGenex. Under the amended agreement, OncoGenex will independently develop and is responsible for all development costs and activities for OGX-011 and we will receive royalties for OGX-011 ranging from 5.5% to 7% of net sales. In addition, OncoGenex will pay us 30% of the upfront fees and milestone payments that OncoGenex receives if OncoGenex licenses OGX-011 prior to initiation of registration trials, 25% if OncoGenex licenses OGX-011 before 20% of patients have been enrolled in a registration trial, 20% if OncoGenex licenses OGX-011 prior to marketing approval and 15% thereafter. In August 2003, the companies entered into a collaboration and license agreement for the development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427, which targets Hsp27. OncoGenex will pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-427.

During 2008, we did not recognize any revenue from our relationship with OncoGenex, compared to $4,000 and $1.2 million for 2007 and 2006, respectively. In August 2008, OncoGenex completed a reverse takeover of Sonus Pharmaceuticals, a publicly traded company, and became a subsidiary of Sonus, which was renamed OncoGenex Pharmaceuticals, Inc. As a result of this transaction, our shares of OncoGenex preferred stock converted into 122,485 shares of OncoGenex common stock, which is traded on the Nasdaq Capital Market. As of December 31, 2008 and 2007, our ownership interest in OncoGenex was less than 10%.

Novosom AG

In August 2008, we granted Novosom an exclusive, worldwide license to access certain antisense inhibitors targeting CD40 mRNA for a number of indications. Novosom plans to target CD40, a well established target for both inflammatory and autoimmune disease, for indications such as Crohn's disease, organ transplant or rheumatoid arthritis. In exchange for the exclusive, worldwide license, Novosom paid us an upfront payment. In addition, assuming Novosom successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $6 million for the achievement of key clinical and regulatory milestones. We will also receive royalties on sales of these antisense drugs Novosom develops. Furthermore, if Novosom sublicenses an antisense drug using our technology, we may be entitled to a portion of the consideration Novosom receives. We have no significant remaining obligations to perform under this agreement. During 2008, we recognized $375,000 in revenue from our relationship with Novosom.

Technology Development Satellite Company Collaborations

In addition to our traditional pharmaceutical alliances and drug discovery and development satellite company partnerships, we also have satellite company partnerships focused on developing and advancing certain RNA-based therapeutic technologies. These partnerships take advantage of our dominant intellectual property estate, and leverage our own investments in our core technologies. These collaborations typically involve a cross-license between us and our partner and allow us to participate in newly emerging approaches to RNA-based therapeutics and augment our active programs in these areas.

Archemix Corp.

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

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, the potential milestone payments from Alnylam total $3.4 million, which Alnylam will pay to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of December 31, 2008, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery. As of December 31, 2008, we had earned a total of $36.1 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners.

During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2008, we no longer own any shares of Alnylam. During 2008, 2007 and 2006, we generated revenue from our relationship with Alnylam totaling $4.6 million, $26.5 million and $750,000, respectively, representing 4%, 45% and 5%, respectively, of our total revenue for those years.

Ercole Biotech, Inc.

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

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

In March 2008, AVI BioPharma, Inc. acquired Ercole's rights and obligations under the collaboration agreement. As a result of our collaboration agreement with Ercole, as part of the acquisition, we received a warrant to purchase 238,228 shares of AVI's common stock at an exercise price of $0.1679 per share, and a warrant to purchase 207,757 shares of AVI's common stock at an exercise price of $3.61 per share. During 2008, 2007 and 2006, we did not recognize any revenue from our relationship with Ercole.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense drugs through, for example, direct delivery to the CNS. These programs represent opportunities for us and our technology, but they currently lie outside our core focus area for internal investment, and therefore we fund these studies through support from our partners or disease advocacy groups and foundations. For example, external funding supports our ALS and Huntington's Disease programs.

CHDI, Inc.

In November 2007, we entered into an agreement with CHDI, which provides us with up to $9.9 million in funding for the discovery and development of an antisense drug for the treatment of Huntington's Disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's Disease. During 2008, 2007 and 2006, we recognized revenue of $2.7 million, $329,000 and $70,000, respectively, from our relationship with CHDI.

Korea Institute of Toxicology

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

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

In October 2005, we entered a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs in the areas of ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration. The researchers from the Ludwig Institute and Center for Neurological Studies, through funding from the ALS Association and the Muscular Dystrophy Association, are conducting IND-enabling preclinical studies of ISIS-$SOD1_{Rx}$. Except for the funding provided by the ALS Association and the Muscular Dystrophy Association, we control and are responsible for funding the continued development of ISIS-$SOD1_{Rx}$.

Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We own or exclusively license more than 1,600 issued patents, which we believe represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our pharmaceutical and satellite company partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies like AMI, Idera Pharmaceuticals, Inc. (formerly Hybridon, Inc.), Integrated DNA Technologies, Inc., Roche Molecular Systems, Silence Therapeutics plc. (formerly Atugen AG), and Dharmacon, Inc. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc., a wholly owned subsidiary of OSI Pharmaceuticals, Inc. To date, we have generated more than $334 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology, including as it relates to our second generation antisense drugs and to double-stranded siRNA therapeutics. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to our suite of RNase H patents.

Integrated DNA Technologies, Inc.

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

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

Abbott Molecular Inc.

In January 2008, we and our former subsidiary, Ibis Biosciences, entered into a Strategic Alliance Master Agreement and a Call Option Agreement with AMI, pursuant to which:

- In 2008, AMI invested $40 million in Ibis providing the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics; and

- We granted AMI an exclusive call option to acquire from us all remaining Ibis capital stock.

In December 2008, AMI exercised the call option and we, Ibis and AMI executed a stock purchase agreement. Under the stock purchase agreement, AMI purchased the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. AMI's initial investments, along with the $175 million AMI paid at closing, resulted in a total acquisition price of $215 million plus the earn out payments described below.

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

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, now a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid us a $2 million upfront fee and agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in milestone payments, and our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. During 2008, 2007 and 2006, because of our agreement with Drug Royalty Trust 3, or DRT, as described below we did not recognize any revenue from our relationship with Eyetech.

Drug Royalty Trust 3, successor in interest to Drug Royalty USA, Inc.

In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA, Inc., who subsequently transferred its interest to DRT. To date, we have received a total of $23 million under this arrangement. We and DRT are sharing the royalty rights on Macugen from Eyetech through 2009. After 2009, we retain all royalties for Macugen. Through 2009, DRT will receive the royalties on the first $500 million of annual sales of Macugen. We and DRT will each receive 50 percent of royalties on annual sales between $500 million and $1 billion. We retain 90 percent of all royalties on annual sales in excess of $1 billion and 100 percent of all royalties after 2009. We have retained all milestones payable to us by Eyetech under the license agreement. During 2008, we did not recognize any revenue under this arrangement, compared to $7 million and $8 million for 2007 and 2006, respectively. As collateral for our obligations under the sale agreement, we granted DRT a first priority security interest in the patents licensed by us to Eyetech under the license agreement and in the license agreement itself.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. During 2008, 2007 and 2006, we recognized revenue of $1.2 million, $807,000 and $200,000, respectively, from our relationship with Roche Molecular Systems.

Regulus Collaborations

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

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

GlaxoSmithKline

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

Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock. Regulus is also eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In addition to the potential of up to nearly $600 million Regulus could receive in license and milestone payments, Regulus would also receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance. For 2008, Regulus recognized revenue of $1.9 million related to Regulus' collaboration with GSK.

Manufacturing

Drug Discovery and Development

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

drug development partners and the clinical successes of our antisense drugs, including mipomersen, we anticipate that we will need to increase our manufacturing capacity. In order to accommodate our increasing demand, we are currently upgrading and optimizing the efficiency of our manufacturing facility. We started this process in 2008 and expect to complete the upgrades in 2009.

Our drug substance manufacturing facility is located in an approximately 28,704 square foot building at 2282 Faraday Avenue, Carlsbad, California. In September 2005, as part of a sale and lease-back transaction, we entered into a lease for this building with an affiliate of BioMed Realty, L.P. The lease has an initial term of fifteen years with an option to extend the lease for up to two five-year periods.

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

Regulus Therapeutics

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

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the United States and other countries. We file applications, as appropriate, claiming products and processes. As of February 1, 2009, we owned or exclusively licensed more than 1,600 issued patents worldwide.

Isis Pharmaceuticals, Inc.

We own or control patents that provide exclusivity for particular products in development and patents that provide exclusivity to our core technology in the field of antisense more generally. Our core technology patents include claims to chemically modified oligonucleotides and antisense drug designs independent of specific cellular target, nucleic acid sequence, or clinical indication. Other patents claim antisense compounds having nucleic acid sequences complementary to cellular target nucleic acids, independent of chemical modifications of the antisense compounds. Finally, claims providing exclusivity for a particular product are more narrowly drawn to combine specific nucleic acid sequences and chemical modifications. We maintain our competitive advantage in the field of antisense technology by protecting our core platform technology and by creating multiple layers of patent protection for each of our potential drug products.

The most broadly applicable Isis patents claim nucleoside modifications and oligonucleotides comprising the modified nucleosides, which help to increase the therapeutic efficacy of antisense drugs. Nucleosides are the basic building blocks of antisense drugs. Since these claims are not limited to a particular oligonucleotide sequence or cellular target, they can reach oligonucleotides useful for any number of clinical indications. Further, these claims reach oligonucleotides that exploit different mechanisms of action, including oligonucleotides useful for RNase H-dependent antisense, RNAi applications, or for altering pre-RNA splicing. For example, U.S. Patent Nos. 5,670,633; 6,005, 087; 6,531,584; and 7,138,517 claim oligonucleotides comprising 2'-modified nucleosides, including 2'-fluoro nucleosides. These modifications may be used in oligonucleotides addressing a variety of gene targets or utilizing different mechanisms of action. Furthermore, claims of U.S. Patent No. 5,914,396 cover oligonucleotides having 2'-methoxyethoxy, or 2'-MOE, nucleosides, the chemical modification we use in our second generation antisense drugs.

Other Isis patents claim oligonucleotides comprising specific antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that make oligonucleotides comprising them particularly suited for a particular cellular mechanism of action. For example, US Patent No. 7,015,315, the '315 patent, claims oligonucleotides comprising a region modified with 2'-O-alkyl substituents, such as 2'-MOE, and a region comprising

deoxyribonucleosides. Oligonucleotides incorporating these motifs, sometimes referred to as chimeric compounds or gapmers are designed to exploit the RNase H mechanism. All of our development compounds, including mipomersen, contain this gapmer antisense drug design motif. In fact, the '315 patent covers each of our second generation development candidate antisense compounds until March of 2023. Similarly, US Patent Nos. 5,898,031, 6,107,094, 7,432,249 and 7,432,250 (the Crooke Patents), cover oligonucleotides comprising methods and motifs useful for exploiting the RNAi pathway until June of 2016. We licensed the Crooke Patents to Alnylam for the development of double-stranded therapeutics and to Regulus for the development of microRNA-based therapeutics.

We also own more than 400 patents, worldwide, with claims to antisense oligonucleotides directed to particular therapeutically important targets or methods of achieving clinical endpoints using antisense oligonucleotides. Many of these patents include claims to any oligonucleotide that hybridizes to the particular target. For example, in 2008, we obtained US Patent No. 7,407,943, which is drawn to the use of both single-stranded and double-stranded antisense drugs complementary to any site of the mRNA of human apoB, regardless of chemistry or antisense mechanism of action. The patent provides broad protection of the Isis-Genzyme apoB franchise, including mipomersen and potential future follow-on compounds. Target patents may also include claims reciting the specific nucleic acid sequences utilized by our products, independent of chemical modifications and motifs. In addition, our product specific patents typically include claims combining specific nucleic acid sequences with nucleoside modifications and motifs. In this way, we seek patent claims narrowly tailored to protect our products specifically, in addition to the broader core antisense patents described above.

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

Regulus Therapeutics

Regulus has been granted exclusive licenses to both our and Alnylam's intellectual property for microRNA applications. This includes a portfolio of over 900 patents and patent applications, of which over 600 are issued, including our patents claiming chemical modification of oligonucleotides for therapeutic applications. In addition, Regulus has acquired rights to a large estate of patents and patent applications accumulated by both us and Alnylam in the field of microRNA therapeutics, including early fundamental patents in the field of microRNAs. Like the Isis portfolio, Regulus owns or controls patents directed to core technology, specific microRNA compounds, and methods of modulating microRNAs for several therapeutic indications. Regulus exclusively controls the therapeutic rights stemming from the discovery of more than 120 mammalian microRNAs by Dr. Thomas Tuschl. The first patent to issue from this patent portfolio, U.S. Patent No. 7,232,806, includes claims to antisense compounds targeted to miR-122. Regulus also has non-exclusive access to additional novel microRNAs discovered by Dr. Thomas Tuschl. Regulus exclusively controls the patent portfolio that originated from Dr. Peter Sarnow's discovery that antagonism of miR-122 affects HCV replication. This patent portfolio has yielded U.S. Patent No. 7,307,067, which claims methods of inhibiting HCV replication in a cell with an oligonucleotide antagonist targeted to miR-122. These Regulus' issued patents protect therapeutic applications of miR-122 until at least September of 2022. Additionally Regulus owns or controls patent portfolios covering other therapeutic applications of microRNA compounds, such as cholesterol lowering and immune response modulation.

Government Regulation

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

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

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

Competition

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

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

Employees

As of February 10, 2009, we employed approximately 300 people. Included in our total number of employees is 22 people within our Regulus subsidiary. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of February 10, 2009:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.....	63	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D	53	Director, Chief Operating Officer, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.....	52	Senior Vice President, Antisense Research
Richard S. Geary, Ph.D.....	51	Senior Vice President, Development

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

Chairman, Chief Executive Officer and President

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

B. LYNNE PARSHALL, J.D.

Director, Chief Operating Officer, Chief Financial Officer and Secretary

Ms. Parshall has served as a Director of Isis since September 2000. She was promoted to Chief Operating Officer in December 2007 and previously served as an Executive Vice President since December 1995. She has served as our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP (now Cooley Godward Kronish LLP), outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations. Ms. Parshall serves on the board of directors of CardioDynamics International Corporation, a publicly held biotechnology company.

C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

Dr. Bennett was promoted to Senior Vice President, Research in January 2006. From June 1995 to January 2006, Dr. Bennett served as our Vice President, Research. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions. He serves on the Scientific Advisory Board of Keystone Symposia, a non-profit organization dedicated to connecting the scientific community for the benefit of society, and is an external member of the Scientific Advisory Board of Experimental Therapeutics Center in Singapore.

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

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

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this Annual Report on Form 10-K 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 Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of December 31, 2008, we had accumulated losses of approximately $839.7 million and stockholders' equity of approximately $67.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Altair, ATL, Atlantic Pharmaceuticals, BMS, iCo, Lilly, Merck, OncoGenex, OMJP and Teva. In addition, in January 2008 we entered a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

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

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

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

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

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

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

For example, a collaborator such as Genzyme, OMJP, or BMS, could determine that it is in its financial interest to:

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

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

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

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

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-cholesterol is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in 2010. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

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

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

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

For example, in December 2006, the European Patent Office (EPO) Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

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

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

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. As of December 31, 2008, we had cash, cash equivalents and short-term investments equal to $491.0 million. This amount does not include the $175 million we received from AMI in January of 2009 in connection with the sale of Ibis. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2008, the market price of our common stock ranged from $9.90 to $20.15 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

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

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

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

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

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

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^5/_8$% convertible subordinated notes, including the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

The continuing deterioration in the global credit markets, the financial services industry and the U.S. capital markets, 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 current economic crisis is uncertain. It is possible that the current 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.

Risks Associated with our Drug Discovery and Development Business

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

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

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

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

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

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

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

- the clinical trial may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;

- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

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

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

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

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

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

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

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

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

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

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

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

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

These competitive developments could make our products obsolete or non-competitive.

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

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

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

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 10, 2009, we occupied approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire in 2010, 2011 and 2012. The leases that expire in 2010 and 2011 have two five-year options to extend the lease while the lease that expires in 2012 has one five-year option to extend the lease. The lease on the building we primarily use for our drug development manufacturing expires in 2020 and has two five-year options to extend the lease.

Item 3. Legal Proceedings

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under our agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery is in its early stage. We will continue to represent and defend Ibis Biosciences in this matter.

Item 4. Submission of Matters to a Vote of Security Holders

Not applicable.

PART II

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

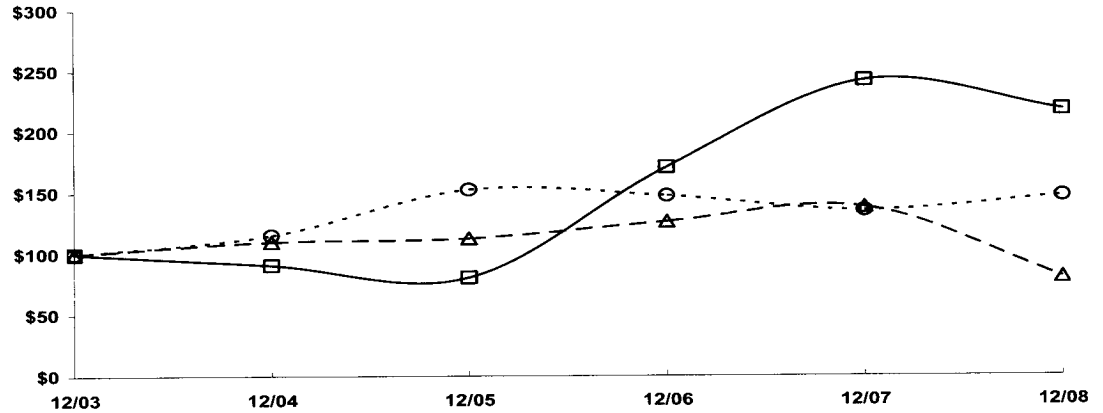
Our common stock is traded publicly through the Nasdaq Global Market under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by the Nasdaq Global Market. These prices do not include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

	HIGH	LOW
2008		
First Quarter	$ 20.15	$ 12.70
Second Quarter	$ 17.77	$ 10.91
Third Quarter	$ 19.29	$ 13.42
Fourth Quarter	$ 16.93	$ 9.90
2007		
First Quarter	$ 12.59	$ 8.30
Second Quarter	$ 10.58	$ 8.79
Third Quarter	$ 15.52	$ 9.52
Fourth Quarter	$ 18.23	$ 14.88

As of February 19, 2009, there were approximately 857 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2003 in our common stock, the NASDAQ Composite Index (total return) and the AMEX Biotech Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



	Dec-03	Dec-04	Dec-05	Dec-06	Dec-07	Dec-08
Isis Pharmaceuticals, Inc.	$ 100	$ 91	$ 81	$ 171	$ 242	$ 218
AMEX Biotech Index	$ 100	$ 115	$ 153	$ 148	$ 135	$ 147
NASDAQ Composite Index	$ 100	$ 110	$ 113	$ 127	$ 138	$ 80

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

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

	Years Ended December 31,				
	2008	2007	2006	2005	2004
Consolidated Statement of Operations Data:					
Revenue(1)	$ 107,190	$ 58,344	$ 14,859	$ 28,340	$ 31,691
Research and development expenses(1)	$ 106,439	$ 78,204	$ 69,411	$ 72,309	$ 108,472
Net loss from continuing operations(1)(2)	$ (3,576)	$ (4,965)	$ (43,003)	$ (74,036)	$ (143,434)
Net loss applicable to common stock(3)	$ (11,963)	$ (136,305)	$ (45,903)	$ (72,401)	$ (142,864)
Basic and diluted net loss per share from continuing operations(1)(2)	$ (0.04)	$ (0.06)	$ (0.58)	$ (1.18)	$ (2.53)
Basic and diluted net loss per share applicable to common stock(3)	$ (0.13)	$ (1.63)	$ (0.62)	$ (1.15)	$ (2.52)
Shares used in computing basic and diluted net loss per share	94,566	83,739	74,308	62,877	56,642

	As of December 31,				
	2008	2007	2006	2005	2004
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments(4)	$ 490,998	$ 193,719	$ 193,333	$ 94,389	$ 103,883
Working capital(4)	$ 393,686	$ 147,669	$ 181,064	$ 82,065	$ 82,193
Total assets	$ 574,150	$ 258,858	$ 255,907	$ 166,373	$ 208,425
Long-term debt and other obligations, less current portion(4)	$ 345,204	$ 186,410	$ 132,866	$ 139,915	$ 236,611
Noncontrolling interest in Symphony GenIsis, Inc.	$ —	$ —	$ 29,339	$ —	$ —
Noncontrolling interest in Regulus Therapeutics Inc.	$ 4,737	$ 9,371	$ —	$ —	$ —
Noncontrolling interest in Ibis Biosciences, Inc.	$ 32,419	$ —	$ —	$ —	$ —
Accumulated deficit	$ (839,708)	$ (827,745)	$ (816,751)	$ (770,848)	$ (698,447)
Stockholders' equity (deficit)	$ 67,092	$ 872	$ 68,563	$ 2,665	$ (72,133)

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

(2) Our net loss from continuing operations and our net loss per share from continuing operations calculation include charges (benefit) related to restructuring activities of ($536,000), $7.0 million and $32.4 million in 2006, 2005 and 2004, respectively.

(3) Our net loss applicable to common stock and our basic and diluted net loss per share applicable to common stock calculation include $125.3 million excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc. in 2007 and accretion of dividends on preferred stock of $361,000 in 2004.

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

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

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. Our highly efficient and prolific drug discovery platform enables us to expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with mature development, commercialization and marketing expertise, such as BMS, Genzyme, Lilly and OMJP. Additionally, we created a consortium of smaller companies that can broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, our jointly owned company focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as our Ibis Biosciences subsidiary, which we recently sold to AMI. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the U.S., ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated more than $334 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology because it demonstrates that antisense drugs can work in man. With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform, increased the value of our drugs, and created renewed interest from potential partners in antisense technology.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Over the past two years, we have established a number of notable pharmaceutical partnerships, which include Genzyme, BMS and OMJP, to develop and commercialize certain of our key cardiovascular and diabetes drugs. Our recent partnerships, including our strategic alliance with AMI, have generated an aggregate of more than $650 million in payments from licensing fees, equity purchase payments and milestone payments with the potential to earn over $2.5 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Business Segments

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

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. Our proprietary drug discovery platform enables us to rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 19 drugs in development. Our partners are licensed to develop, with our support, 15 of these 19 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

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

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for 2008 and all prior periods in our financial statements separately as discontinued operations and therefore Ibis is no longer included in our segment reporting.

Critical Accounting Policies

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

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

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in available-for-sale securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;

- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include SAB 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and EITF 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

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

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

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we have no future performance obligations related to achieving the milestone. In September 2007, we earned a $5 million milestone payment for the initiation of a Phase 1 trial for OMJP-GCGR$_{Rx}$ under our collaboration with OMJP. Since we achieved the milestone before we finalized the contract, we treated the $5 million as an upfront licensing fee and we are amortizing it over the two year period of our performance obligation. In April 2008, BMS selected a development candidate, BMS-PCSK9$_{RX}$, for which we earned a $2 million milestone payment. Most recently, in early 2009, we received a $1 million milestone payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, because Achaogen filed an IND for its aminoglycoside drug, ACHN-490. Because we do not recognize revenue when we receive equity in private companies, we will recognize $500,000 of this milestone in the first quarter of 2009.

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that we had met the provisions in SAB 104 before we recognized the related revenue.

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

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

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

Valuation of Investments in Marketable Securities

We classify our securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities*. We carry our available-for-sale securities at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include gross realized gains and losses in investment income. We use the specific identification method to determine the cost of debt securities sold.

We also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. 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 issuer, near term prospects of the issuer, and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting according to Accounting Principles Board 18, *The Equity Method of Accounting for Investments in Common Stock.* When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During 2008, we recognized a $965,000 loss on investments consisting of a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex and a $198,000 gain that we realized on our available-for-sale securities. See further discussion about our investment in OncoGenex in *Note 7, Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements. During 2007, we sold the remainder of our equity securities of Alnylam that we owned resulting in a realized gain of $3.5 million, compared to a net gain on investments of $2.3 million during 2006. The net gain on investments during 2006 represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we owned, offset by a non-cash loss of $465,000 related to the other-than-temporary impairment of our equity investment in ATL. We determined that there were no other-than-temporary declines in value of our investments in 2007.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets* and we evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties to determine if any impairment is present. We consider the following factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;

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

We recorded a charge of $1.9 million, $887,000 and $2.8 million for 2008, 2007 and 2006, respectively, primarily related to the assignment of patents to certain of our partners and the write-down of equipment and intangible assets to their estimated net realizable values.

Valuation of Inventory

In accordance with SFAS 2, *Accounting for Research and Development Costs*, we capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver our drugs to 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 our 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 lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

We record a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. We have had net operating losses since inception, and as a result, we have established a 100% valuation allowance for our net deferred tax asset. When and if circumstances warrant, we will assess the likelihood that we will more likely than not recover our net deferred tax assets from future taxable income and record an appropriate reversal to the valuation allowance.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Regulus subsidiary based on the segregation of revenues and expenses we use for management's assessment of operating performance and operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments. We have not made material changes to our allocation methodologies since we began reporting segment financial information and results. Different assumptions or allocation methods could result in materially different results by segment. Prior to announcing the sale of Ibis to AMI, we reported Ibis as a separate segment. In accordance with SFAS 144, we now report Ibis as discontinued operations for all periods we present in our consolidated financial statements.

Stock-Based Compensation

On January 1, 2006, we adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our employee stock purchase plan based on estimated fair values. In March 2005, the SEC issued SAB 107, *Share-Based Payment*, relating to SFAS 123R. We have applied the provisions of SAB 107 in our adoption of SFAS 123R.

As of December 31, 2008, total unrecognized compensation cost related to non-vested stock-based compensation plans was $14.3 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.3 years.

We utilize the Black-Scholes model and assumptions discussed in *Note 5, Stockholders' Equity,* in the Notes to the Consolidated Financial Statements, for estimating the fair value of the stock-based awards we granted. We recognize compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. We base our risk-free interest rate assumption on observed interest rates appropriate for the term of our employee stock options and our Employee Stock Purchase Plan, or ESPP. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123R. The expected term of stock options granted represents the period of time that we expect them to be outstanding.

For our 2002 Non-Employee Directors' Stock Option Plan and for stock options granted on or after January 1, 2008 for our employee stock option plans, we estimate the expected term of options granted based on historical exercise patterns. For the stock options granted prior to January 1, 2008 for our employee stock option plans, we determine the estimated expected term as a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. There were no material changes to our estimated forfeitures for 2008, 2007 and 2006.

We record stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, at their fair value in accordance with the requirements of SFAS 123R, then periodically remeasure them in accordance with EITF 96-18, *Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, and recognize them over the service period.

Results of Operations

Years Ended December 31, 2008 and December 31, 2007

Revenue

Total revenue for the year ended December 31, 2008 was $107.2 million, compared to $58.3 million for 2007. The significant increase in 2008 revenue over 2007 was a result of our new collaborations. As part of our strategic relationship with Genzyme, Genzyme purchased $150 million of our common stock at $30 per share and in the second quarter paid us a licensing fee of $175 million. We are amortizing the premium on the stock, $100 million calculated using a Black-Scholes option valuation model, and the licensing fee ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement.

Period to period fluctuations in our revenue are common because the nature and timing of payments under agreements with our partners, including license fees and milestone payments, significantly affects our revenue. For example, in 2007, we earned $26.5 million of licensing revenue from Alnylam's sublicense of our technology for the development of RNA interference therapeutics to Roche, while in 2008, we earned $6.1 million in sublicensing revenue from Alnylam and ATL.

Collaborations with Genzyme, OMJP, BMS and Regulus' strategic alliance with GSK include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received and from research and development funding.

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

	Year Ended December 31,	
	2008	2007
Drug Discovery and Development:		
Research and development revenue	$ 96,743	$ 22,200
Licensing and royalty revenue	8,337	36,025
	$ 105,080	$ 58,225
Regulus Therapeutics:		
Research and development revenue	$ 2,110	$ 119
	$ 2,110	$ 119
Total revenue:		
Research and development revenue	$ 98,853	$ 22,319
Licensing and royalty revenue	8,337	36,025
	$ 107,190	$ 58,344

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

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

Licensing and Royalty Revenue

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

Regulus Therapeutics

Regulus' revenue for the year ended December 31, 2008 was $2.1 million, compared to $119,000 for 2007. The increase was primarily due to revenue from its collaboration with GSK. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which Regulus began amortizing into revenue in the second quarter of 2008 and will continue to amortize over Regulus' six year period of performance under the agreement.

Operating Expenses

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

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

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

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

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

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs. Also included in research and development expenses are Regulus' research and development expenses. The following table sets forth information on research and development costs (in thousands):

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

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

	Year Ended December 31,	
	2008	2007
Drug Discovery and Development	$ 89,334	$ 70,863
Regulus Therapeutics	6,527	596
Non-cash compensation expense related to stock options	10,578	6,745
Total research and development expenses	$ 106,439	$ 78,204

For the year ended December 31, 2008, we incurred total research and development expenses, excluding stock compensation, of $95.9 million, compared to $71.5 million for 2007. We attribute the increase in expenses to the expansion of our key programs and Regulus' research activities. We discuss expenses related to Regulus in a separate section below. Going forward, our research and development expenses will increase modestly as we continue the development of mipomersen, as Regulus continues to build its core team, and as we expand our research and development efforts in different disease areas.

Drug Discovery & Development

Antisense Drug Discovery

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

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

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

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

Antisense Drug Development

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

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

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

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 15 of our 19 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we will over time transition the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We will contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable.

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

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

R&D Support

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

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

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

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

General and Administrative Expenses

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 business development, legal, human resources, investor relations, finance and Regulus' general and administrative expenses, which began in September 2007 when we and Alnylam formed Regulus. 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. Until our acquisition of Symphony GenIsis in September 2007, general and administrative expenses also included Symphony GenIsis' general and administrative expenses.

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

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

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

	Year Ended December 31,	
	2008	2007
Drug Discovery and Development	$ 10,011	$ 11,490
Regulus Therapeutics	1,092	16
Non-cash compensation expense related to stock options	2,708	1,553
Total general and administrative expenses	$ 13,811	$ 13,059

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

Regulus Therapeutics

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

	Year Ended December 31,	
	2008	2007
Research and development expenses	$ 6,525	$ 596
General and administrative expenses	1,092	16
Non-cash compensation expense related to stock options	2,414	412
Total Regulus' operating expenses	$ 10,031	$ 1,024

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

Investment Income

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

Interest Expense

Interest expense for the year ended December 31, 2008 totaled $5.6 million, compared to $7.6 million for 2007. The decrease in interest expense was due to the effect of a lower average debt balance in 2008 compared to 2007 primarily related to the fact that a portion of our old $5^1/_2$% notes was outstanding until we repaid the remaining balance in May 2007.

In 2009, when we adopt the new convertible debt accounting standard, FSP No. APB 14-1, we anticipate that the amount of interest expense that we record in our statement of operations will increase due to the non-cash amortization of the debt discount. For additional information about FSP No. APB 14-1, see *Note 1, Organization and Significant Accounting Policies,* in the Notes to the Condensed Consolidated Financial Statements.

Gain (Loss) on Investments, net

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

Loss on Early Retirement of Debt

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

Net Loss from Continuing Operations

Net loss from continuing operations for the year ended December 31, 2008 was $3.6 million compared to $5.0 million for 2007. The decrease in net loss from continuing operations was a result of a decrease in loss from operations in 2008 offset by a benefit of $23.2 million we recognized in 2007 for the loss attributed to noncontrolling interest in Symphony GenIsis, related to our collaboration with Symphony GenIsis. Additionally, we recognized a benefit of $4.7 million and $629,000 for the loss attributed to noncontrolling interest in Regulus for the years ended December 31, 2008 and 2007, respectively.

Net Loss from Discontinued Operations

In January 2008, we, Ibis and AMI entered into a strategic alliance. As part of the strategic alliance, in 2008, AMI purchased approximately 18.6% of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement. Under this agreement, AMI purchased the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. See *Note 7—Collaborative Arrangements and Licensing Agreements*, in the Notes to the Condensed Consolidated Financial Statements, for additional information about our strategic alliance with AMI.

We reflect Ibis as discontinued operations because Ibis meets the criteria for a component of an entity under SFAS 144. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net loss from discontinued operations for the year ended December 31, 2008 was $8.4 million compared to $6.0 million for 2007. The increase in net loss from discontinued operations in 2008 compared to 2007 primarily relates to an increase in expenses to support the growth of Ibis' commercial business including selling and support costs for the Ibis T5000 Biosensor System and the cost to achieve milestones as part of the AMI transaction partly offset by the gain recognized for the revaluation of the subscription right and call option we granted to AMI and a benefit of $2.1 million for the loss attributed to noncontrolling interest in Ibis for 2008.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the year ended December 31, 2008 was $12.0 million compared to $136.3 million for 2007. In 2007, we purchased the equity of Symphony GenIsis. The $125.3 million on our Consolidated Statement of Operations in the line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend paid to the previous owners of Symphony GenIsis. This deemed dividend only impacts our net loss applicable to common stock and our net loss per share calculations for 2007 and does not affect our net loss from continuing operations or discontinued operations.

Net Loss per Share Applicable to Common Stock

Net loss per share for the year ended December 31, 2008 was $0.13 per share, compared to $1.63 per share for 2007, of which $1.50 per share was attributable to the purchase of Symphony GenIsis. The decrease in net loss per share for 2008 compared to 2007 was primarily a result of the decrease in net loss applicable to common stock discussed above.

Net Operating Loss Carryforward

At December 31, 2008, we had federal, California and foreign tax net operating loss carryforwards of approximately $591.1 million, $180.6 million and $1.1 million, respectively. We also had federal and California research credit carryforwards of approximately $31.3 million and $22.2 million, respectively. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal and California tax loss carryforwards will continue to expire in 2008 and 2013, respectively, unless previously utilized. Our foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Years Ended December 31, 2007 and December 31, 2006

Revenue

Total revenue for the year ended December 31, 2007 was $58.3 million, compared to $14.9 million for 2006. Revenue was higher in 2007 compared to 2006 due to the $26.5 million sublicensing revenue that we earned from Alnylam in the third quarter of 2007 and revenue associated with our collaborations with BMS, which began in May 2007, and OMJP, which began in September 2007.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the year ended December 31, 2007 was $22.3 million, compared to $5.4 million for 2006. The increase reflects revenue associated with our collaborations with BMS and OMJP offset by a decrease in revenue associated with our collaborations with Lilly and OncoGenex.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the year ended December 31, 2007 was $36.0 million, compared to $9.4 million for 2006. The increase was primarily a result of the $26.5 million sublicensing revenue that we earned from Alnylam in 2007.

Operating Expenses

In 2007, as our drugs advanced into and through development, we expanded our clinical development programs. These activities led to an increase in operating expenses for 2007 compared to 2006. Operating expenses for the year ended December 31, 2007 were $91.3 million, compared to $80.1 million for 2006. Also contributing to the increase in operating expenses was an increase in non-cash compensation expense. Non-cash compensation expense related to stock options was $8.3 million for the year ended December 31, 2007, compared to $4.8 million for 2006, primarily reflecting the significant increase in our stock price from period to period.

Our operating expenses were as follows (in thousands):

	Year Ended December 31,	
	2007	2006
Drug Discovery and Development	$ 91,263	$ 80,613
Corporate	—	(536)
Total operating expenses	$ 91,263	$ 80,077

Research and Development Expenses

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

	Year Ended December 31,	
	2007	2006
Research and development expenses	$ 71,459	$ 65,617
Non-cash compensation expense related to stock options	6,745	3,794
Total research and development as reported	$ 78,204	$ 69,411

For the year ended December 31, 2007, we incurred total research and development expenses, excluding stock compensation, of $71.5 million, compared to $65.6 million for 2006. We attribute the increase to the expansion of our key programs.

Drug Discovery & Development

Antisense Drug Discovery

Antisense drug discovery costs excluding non-cash compensation expense were $14.8 million for the year ended December 31, 2007, compared to $13.5 million for 2006. The higher expenses in 2007 were primarily due to an increase in personnel and lab supplies costs related to increased activity levels.

Antisense Drug Development

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

	Year Ended December 31,	
	2007	2006
Alicaforsen for Crohn's disease	$ —	$ 5
Other antisense development products	24,731	21,205
Development overhead costs	5,700	4,183
Non-cash compensation expense related to stock options	2,731	1,468
Total antisense drug development	$ 33,162	$ 26,861

Antisense drug development expenditures were $30.4 million, excluding non-cash compensation expense, for the year ended December 31, 2007 compared to $25.4 million for 2006. The increase was primarily attributed to the expansion of our clinical development programs including multiple Phase 2 trials for mipomersen, which led to an increase in development costs in 2007 compared to 2006. Development overhead costs were $5.7 million for the year ended December 31, 2007, compared to $4.2 million for 2006. The increase in overhead costs was a result of the additional expenses needed to support the expansion of our clinical development programs.

Manufacturing and Operations

Manufacturing and operations expenses excluding non-cash compensation expense for the year ended December 31, 2007 were $7.1 million, compared to $6.1 million for 2006. The increase was primarily due to the additional drug required to support our expanded clinical development programs and the additional costs associated with the manufacturing of drug supplies for our corporate partners.

R&D Support

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

	Year Ended December 31,	
	2007	2006
Personnel costs	$ 5,387	$ 5,561
Occupancy	6,056	5,868
Depreciation and amortization	4,987	6,955
Insurance	960	995
Other	1,711	1,227
Non-cash compensation expense related to stock options	1,685	910
Total R&D support costs	$ 20,786	$ 21,516

R&D support costs excluding non-cash compensation expense for the year ended December 31, 2007 were $19.1 million, compared to $20.6 million for 2006. The decrease from 2006 to 2007 was primarily a result of a decrease in patent application costs that we abandoned and wrote-off during 2006.

General and Administrative Expenses

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

	Year Ended December 31,	
	2007	2006
General and administrative expenses	$ 11,506	$ 10,233
Non-cash compensation expense related to stock options	1,553	969
Total general and administrative as reported	$ 13,059	$ 11,202

General and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2007 were $11.5 million, compared to $10.2 million for 2006. The increase in expenses was primarily the result of higher external legal fees we incurred in 2007 in connection with our arbitration proceeding with Idera, which ended in January 2008 when we prevailed in the matter, personnel costs and the consolidation of Regulus' general and administrative expenses into our financial results.

Restructuring Activities

During the year ended December 31, 2006, we recorded a benefit of $536,000 for restructuring activities resulting from our decision to focus our resources on key programs.

In 2006, we successfully negotiated a contract modification settlement with one of our vendors. The amount of the contract termination cost was $265,000 less than the amount we had previously accrued. Additionally, we negotiated a lease termination agreement with the landlord of a building that we vacated in 2005 as part of the restructuring activities. The early termination of the lease resulted in a benefit of approximately $350,000 over what we had previously accrued. These benefits were included in the restructuring activities for the year ended December 31, 2006.

Investment Income

Investment income for the year ended December 31, 2007 totaled $11.4 million, compared to $6.0 million for 2006. The increase in investment income was primarily due to a higher average cash balance in 2007 compared to 2006 as a result of the proceeds we received from the issuance of our $2^5/_8\%$ convertible subordinated notes, the $15 million upfront licensing fee received from BMS, the $26.5 million sublicensing fee received from Alnylam, the $10 million invested in Regulus, the $52 million upfront licensing fee, milestone payment and initial research and development funding received from our collaboration with OMJP and the $10.3 million from stock options exercised in 2007, offset by the repayment of our $5^1/_2\%$ notes and the $80.4 million payment for the acquisition of Symphony GenIsis.

Interest Expense

Interest expense for the year ended December 31, 2007 totaled $7.6 million, compared to $9.0 million for 2006. The decrease in interest expense was primarily because we fully repaid our 5 1/2% notes in the first half of 2007 and the 2 5/8% notes we issued in early 2007 have a significantly lower interest rate.

Gain on Investments, net

Gain on investments for the year ended December 31, 2007 was $3.5 million compared to $2.3 million for 2006. The 2007 gain on investments reflected the gain we realized on the sale of the remaining equity securities of Alnylam that we owned compared to the 2006 gain of $2.7 million we realized on the sale of a portion of the equity securities of Alnylam that we owned, offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in ATL.

Loss on Early Retirement of Debt

In January 2007, we issued $162.5 million of 2 5/8% convertible subordinated notes due 2027. Using a portion of the net proceeds from the issuance of these 2 5/8% notes, we repurchased our 5 1/2% convertible subordinated notes due 2009. We recognized a loss of $3.2 million in 2007 as a result of the early repayment of the 5 1/2% notes of which $1.2 million was a non-cash write-off of unamortized debt issuance costs. There was no loss on early retirement of debt in 2006.

Net Loss from Continuing Operations

Net loss from continuing operations for the year ended December 31, 2007 was $5.0 million compared to $43.0 million for 2006. Our net loss for 2007 was lower compared to 2006 because of a decrease in loss from operations, higher interest income, lower interest expense and an increase in net gain on investments offset by the loss on early retirement of debt. In addition, we recognized a benefit of $23.2 million and $23.0 million for the years ended December 31, 2007 and 2006, respectively, in the loss attributed to noncontrolling interest in Symphony GenIsis and a benefit of $629,000 in the loss attributed to noncontrolling interest in Regulus for 2007.

Net Loss from Discontinued Operations

Net loss from discontinued operations increased from $2.9 million to $6.0 million for the years ended December 31, 2006 and 2007, respectively, primarily reflecting an increase in expenses necessary to support commercialization of the Ibis T5000 Biosensor System.

Net Loss Applicable to Common Stock

We purchased the equity of Symphony GenIsis at the pre-negotiated price of $120 million, which we paid with $80.4 million in cash and approximately 3.4 million shares of our common stock. The $125.3 million on our Consolidated Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis represents a deemed dividend to the previous owners of Symphony GenIsis, a portion of which was non-cash. A portion of the $125.3 million reflects the significant increase in our stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts our net loss applicable to common stock and our net loss per share calculations and does not affect our net loss from continuing operations or discontinued operations. Net loss applicable to common stock for the year ended December 31, 2007 was $136.3 million compared to $45.9 million for 2006.

Net Loss per Share

Net loss per share for the year ended December 31, 2007 was $1.63 per share, of which $1.50 per share was attributable to the purchase of Symphony GenIsis, compared to $0.62 per share for 2006.

Net Operating Loss Carryforward

At December 31, 2007, we had federal, foreign and California tax net operating loss carryforwards of approximately $565.2 million, $1.1 million, and $210.0 million, respectively. We also had federal and California research credit carryforwards of approximately $25.9 million and $19.2 million, respectively. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal tax loss carryforwards

began expiring in 2007. Our foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. Our California tax loss carryforwards and our research credit carryforwards began expiring in 2005 and 2006, respectively. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2008, we have earned approximately $697.1 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through December 31, 2008, we have raised net proceeds of approximately $802.9 million from the sale of our equity securities and we have borrowed approximately $555.8 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2008, we had cash, cash equivalents and short-term investments of $491.0 million, which does not include the $175 million we received from AMI in January of 2009 in connection with the sale of Ibis, and stockholders' equity of $67.1 million. In comparison, we had cash, cash equivalents and short-term investments of $193.7 million and stockholders' equity of $872,000 as of December 31, 2007. At December 31, 2008, we had consolidated working capital of $393.7 million, compared to $147.7 million at December 31, 2007. The cash we received in the first half of 2008 from Genzyme ($325.0 million), AMI ($40.5 million) and GSK ($20.0 million) primarily led to the increase in our consolidated working capital offset by $68.9 million of deferred revenue from Genzyme and GSK that we included in current liabilities at December 31, 2008.

As of December 31, 2008, our debt and other obligations totaled $174.5 million, compared to $170.1 million at December 31, 2007. The increase in our debt and other obligations was due to our $6.5 million equipment financing arrangement and the $5 million convertible promissory note Regulus issued to GSK partly offset by the pay off of the Silicon Valley Bank term loan. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of December 31, 2008. 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**
2 5/8% Convertible Subordinated Notes	$ 162.5	$ —	$ —	$ —	$ 162.5
GSK Convertible Promissory Note, including accrued interest	$ 5.2	$ —	$ 5.2	$ —	$ —
Equipment Financing Arrangement	$ 6.5	$ 2.1	$ 4.4	$ —	$ —
Other Obligations	$ 0.3	$ —	$ —	$ —	$ 0.3
Operating Leases	$ 17.7	$ 3.1	$ 4.5	$ 2.3	$ 7.8

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a convertible promissory note from GSK, an equipment financing arrangement and other obligations.

In December 2003, we obtained a $32.0 million term loan from Silicon Valley Bank, which was scheduled to mature in December 2008. In September 2008, we fully paid the remaining principal balance of $1.8 million plus accrued but unpaid interest.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. The $162.5 million convertible subordinated notes bear interest at 2 5/8%, which is payable semi-annually, and mature in 2027. The 2 5/8% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2 5/8% notes are also able to require us to repurchase the 2 5/8% notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2 5/8% notes being repurchased plus accrued interest and unpaid interest. Using the net proceeds from the issuance of our 2 5/8% notes, in 2007, we repaid the entire $125 million of our 5 1/2% convertible subordinated notes due 2009.

In connection with the strategic alliance with GSK in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25% at December 31, 2008. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock.

In October 2008, we entered into a loan agreement related to an equipment financing. Under the loan agreement, we may borrow up to $10 million in principal to finance the purchase of equipment. Each loan under the loan agreement will have a term of approximately three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4%, which was 7.22% at December 31, 2008. We are using the equipment purchased under the loan agreement as collateral. The carrying balance under this loan agreement at December 31, 2008 was $6.5 million. Under the same loan agreement, Ibis borrowed $600,000 in principal to finance the purchase of equipment. The carrying balance under this loan agreement at December 31, 2008 was $585,000 and was included in the liabilities held for sale line item within the accompanying Consolidated Balance Sheet. We expect to draw down the remaining unused portion of this loan agreement in the first quarter of 2009.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2008 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, 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.

Primarily as a result of the significant upfront funding that we received from our strategic alliance with Genzyme in 2008 and the gain we will recognize on the sale of Ibis to AMI, we anticipate having significant taxable income in 2009. To minimize our federal income tax liability, we plan to use our net operating loss carryforwards to offset a majority of our taxable income. Pursuant to Internal Revenue Code Sections 382 and 383, annual usage of our net operating loss and credit carryforwards to offset future taxable income may be limited due to changes in ownership of more than 50%. For our California taxes, the recent tax law changes that were enacted with the 2008/2009 California Budget have suspended our ability to use net operating loss carryforwards for tax years ending in 2008 and 2009. We intend to offset our California income tax liability to the full extent allowed under the tax regulations with our research and development tax credits, which is limited to 50% of the California liability. As a result, we anticipate having a larger tax liability in 2009, which will require us to make estimated tax payments starting in April 2009.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

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

Item 8. Financial Statements and Supplementary Data

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

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

There have been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2008 with our Independent Registered Public Accounting Firm.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

Based on our evaluation as of the end of the period covered by this report on Form 10-K, our principal executive officer and principal financial officer have concluded that our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")) were effective as of December 31, 2008 to ensure that information required to disclose in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms.

Changes in Internal Control over Financial Reporting

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

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2008, management, with the participation of the chief executive officer and chief financial officer, assessed the effectiveness of Isis' internal control over financial reporting based on the criteria for effective internal control over financial reporting established in "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations (COSO) of the Treadway Commission. Based on the assessment, management determined that Isis maintained effective internal control over financial reporting as of December 31, 2008.

The effectiveness of our internal control over financial reporting as of December 31, 2008 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their attestation report, which is included elsewhere herein.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

We have audited Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2008, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Isis Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an

understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

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

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

In our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2008, 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, 2008 and 2007, and the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2008 of Isis Pharmaceuticals, Inc. and our report dated February 23, 2009, expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
February 23, 2009

Item 9B. Other Information

Not applicable

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee by reference from the information under the caption "Election of Directors," "Nominating, Governance and Review Committee" and "Audit Committee," respectively, contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 6, 2009 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2009 Annual Meeting of Stockholders to be held on June 2, 2009.

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

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2008.

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)	6,165,000	$ 9.16	4,084,000(c)
Equity compensation plans not approved by stockholders(b)	3,151,000	$ 13.09	277,000
Total	9,316,000	$ 10.49	4,361,000

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

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below.

(c) Of these shares, 190,976 remained available for purchase under the ESPP as of December 31, 2008. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year through and including 2009, we automatically increase the aggregate number of shares reserved for issuance under the plan by 200,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

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

As of December 31, 2008, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 3,151,000 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 2,562,000 shares had been exercised under the 2000 Plan, and 277,000 shares remained available for grant thereunder.

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% per year after the first year and then at the rate of 2.08% per month thereafter during the option holder's employment or service as a consultant, employee or director. Options granted pursuant to the April 2003 stock option exchange program as discussed in the Notes to the Consolidated Financial Statements, expired on December 31, 2008. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities

subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

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

In the event of:

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

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

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

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

Item 14. Principal Accountant Fees and Services

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

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 63.

(b) Exhibits

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

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 26th day of February, 2009.

ISIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 26, 2009
/s/ B. LYNNE PARSHALL Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	February 26, 2009
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 26, 2009
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	February 26, 2009
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 26, 2009
/s/ FREDERICK T. MUTO Frederick T. Muto	Director	February 26, 2009
/s/ JOHN C. REED, M.D. PH.D. John C. Reed, M.D., Ph.D.	Director	February 26, 2009
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 26, 2009

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(3)
3.3	Bylaws.(19)
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.2	Specimen Common Stock Certificate.(1)
4.3	Form of Right Certificate.(17)
4.4	Stock Purchase Agreement between the Registrant and Genzyme Corporation dated January 7, 2008. (8)
4.5	Indenture, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2 5/8% Convertible Subordinated Note due 2027.(14)
4.6	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein.(14)
4.7	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted).(3)
4.8	Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC.(3)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2*	Registrant's 1989 Stock Option Plan, as amended.(2)
10.3*	Registrant's Employee Stock Purchase Plan.(10)
10.4	Form of Employee Assignment of Patent Rights.(1)
10.5*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.6	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.7	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.8	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.9	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.10	License and Co-Development Agreement between the Registrant and Genzyme Corporation dated June 24, 2008 (with certain confidential information deleted). (12)
10.11	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.12	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008 (with certain confidential information deleted).(8)

10.13 License Agreement between the Registrant and Atlantic Healthcare (UK) Limited dated March 7, 2007 (with certain confidential information deleted).(5)

10.14 VLA4 Partner Support Agreement between the Registrant and Teva Pharmaceutical Industries Ltd dated February 8, 2008 (with certain confidential information deleted).(8)

10.14 Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. (with certain confidential information deleted) (22)

10.16 Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)

10.17 Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)

10.18 License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)

10.19 Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(23)

10.20* Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan.(13)

10.21* Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(29)

10.22 Product Development and Commercialization Agreement between Regulus Therapeutics LLC and Glaxo Group Limited dated April 17, 2008 (with certain confidential information deleted). (12)

10.23* Amendment No. 1 to Isis Pharmaceuticals, Inc. Employee Stock Purchase Plan.(28)

10.24* Amended and Restated Severance Agreement dated December 3, 2008 between Isis and Stanley T. Crooke. (21)

10.25* Amended and Restated Severance Agreement dated December 3, 2008 between Isis and B. Lynne Parshall. (21)

10.26 Strategic Collaboration and License Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(18)

10.27 Amendment No. 1 to Sale Agreement dated October 14, 2007 between Isis and DRT 3.(15)

10.28 Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc.

10.29 Amendment No. 1 to License Agreement between the Registrant and Eyetech.(16)

10.30 Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(16)

10.31 Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(16)

10.32* Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(16)

10.33* Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(16)

10.34* Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(16)

10.35* Employment Agreement dated December 29. 2008 between Regulus Therapeutics and Kleanthis G. Xanthopoulos, PhD

10.36 Amendment No.1 to Rights Agreement dated April 7, 2005.(27)

10.37 Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted).(26)

10.38 Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(23)

10.39 Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(23)

10.40 Pre-Clinical Development Collaboration Agreement dated March 23, 2007 between the Registrant and Korean Institute of Toxicology (with certain confidential information deleted).

10.41 Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. (with certain confidential information deleted).

10.42 Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(14)

10.43 Collaboration and License Agreement between the Registrant and Bristol-Myers Squibb Company dated May 8, 2007 (with certain confidential information deleted). (7)

10.44 Research Agreement dated October 22, 2007 between the Registrant and CHDI, Inc. (with certain confidential information deleted).(4)

10.45 Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007 (with certain confidential information deleted).(20)

10.46 License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).(20)

14.1 Registrant's Code of Ethics and Business Conduct.(21)

21.1 List of Subsidiaries for the Registrant.

23.1 Consent of Independent Registered Public Accounting Firm.

24.1 Power of Attorney.(30)

31.1 Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.

31.2 Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.

32.1 Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

99.2 Form of Confidentiality Agreement.(11)

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(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 Notice of Annual Meeting and Proxy Statement for the 2008 Annual Meeting of Stockholders, filed with the SEC on April 18, 2008, and incorporated herein by reference.

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

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

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2007 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.

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

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

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

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

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

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

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

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

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

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

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

(18) Filed as Exhibit 10.24 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

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

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

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

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

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

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

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

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

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

(28) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended September 30, 2003 and incorporated herein by reference.

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

(30) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2008, reference is made to page 62.

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

ISIS PHARMACEUTICALS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2008 and 2007, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2008. 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, 2008 and 2007, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2008, 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), the effectiveness of Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2008, based on criteria established in Internal Control- Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 23, 2009 expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
February 23, 2009

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

	December 31, 2008	December 31, 2007
ASSETS		
Current assets:		
Cash and cash equivalents	$ 217,918	$ 138,614
Short-term investments	273,080	55,105
Contracts receivable	4,121	4,861
Inventories	2,718	1,762
Other current assets	5,085	3,158
Assets held for sale (including cash and cash equivalents of $6.1 million and $0 as of December 31, 2008 and 2007, respectively)	15,462	6,374
Total current assets	518,384	209,874
Property, plant and equipment, net	17,371	5,960
Licenses, net	16,861	19,100
Patents, net	16,260	16,430
Deposits and other assets	5,274	7,494
Total assets	$ 574,150	$ 258,858
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,710	$ 2,568
Accrued compensation	6,835	8,758
Accrued liabilities	9,556	5,213
Current portion of long-term obligations	2,065	7,238
Current portion of deferred contract revenue	92,662	31,535
Liabilities held for sale	7,870	6,893
Total current liabilities	124,698	62,205
2 5/8% convertible subordinated notes	162,500	162,500
Long-term obligations, less current portion	9,938	362
Long-term deferred contract revenue	172,766	23,548
Total liabilities	469,902	248,615
Noncontrolling interest in Regulus Therapeutics Inc.	4,737	9,371
Noncontrolling interest in Ibis Biosciences, Inc. — Held for sale	32,419	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 97,172,380 and 87,239,423 shares issued and outstanding at December 31, 2008 and 2007, respectively	97	87
Additional paid-in capital	905,721	827,992
Accumulated other comprehensive income	982	538
Accumulated deficit	(839,708)	(827,745)
Total stockholders' equity	67,092	872
Total liabilities, noncontrolling interest and stockholders' equity	$ 574,150	$ 258,858

See accompanying notes.

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

	Years Ended December 31,		
	2008	2007	2006
Revenue:			
Research and development revenue under collaborative agreements	$ 98,853	$ 22,319	$ 5,418
Licensing and royalty revenue	8,337	36,025	9,441
Total revenue	$ 107,190	58,344	14,859
Expenses:			
Research and development	106,439	78,204	69,411
General and administrative	13,811	13,059	11,202
Restructuring activities	—	—	(536)
Total operating expenses	120,250	91,263	80,077
Loss from operations	(13,060)	(32,919)	(65,218)
Other income (expense):			
Investment income	11,318	11,443	5,960
Interest expense	(5,603)	(7,573)	(9,029)
Gain (loss) on investments, net	(965)	3,510	2,263
Loss on early retirement of debt	—	(3,212)	—
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	23,157	23,021
Loss attributed to noncontrolling interest in Regulus Therapeutics Inc	4,734	629	—
Net loss from continuing operations	(3,576)	(4,965)	(43,003)
Net loss from discontinued operations	(8,387)	(6,029)	(2,900)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc	—	(125,311)	—
Net loss applicable to common stock	$ (11,963)	$ (136,305)	$ (45,903)
Basic and diluted net loss per share from continuing operations	$ (0.04)	$ (0.06)	$ (0.58)
Basic and diluted net loss per share applicable to common stock	$ (0.13)	$ (1.63)	$ (0.62)
Shares used in computing basic and diluted net loss per share	94,566	83,739	74,308

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2008, 2007 and 2006
(In thousands)

Description	Common stock Shares	Common stock Amount	Additional paid in capital	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2005	72,201	$ 72	$ 770,263	$ 3,178	$ (770,848)	$ 2,665
Comprehensive Loss:						
Net loss applicable to common stock	—	—	—	—	(45,903)	(45,903)
Change in unrealized gains	—	—	—	1,100	—	1,100
Comprehensive loss	—	—	—	—	—	(44,803)
Options exercised and employee stock purchase plan	1,883	2	11,518	—	—	11,520
Warrants exercised	229	—	—	—	—	—
Share-based compensation expense	—	—	5,747	—	—	5,747
Issuance of common stock under Azimuth equity financing	7,971	8	74,836	—	—	74,844
Issuance of warrants to Symphony Capital	—	—	18,590	—	—	18,590
Balance at December 31, 2006	82,284	$ 82	$ 880,954	$ 4,278	$ (816,751)	$ 68,563
Comprehensive Loss:						
Net loss	—	—	—	—	(10,994)	(10,994)
Change in unrealized losses	—	—	—	(3,740)	—	(3,740)
Comprehensive loss	—	—	—	—	—	(14,734)
Options exercised and employee stock purchase plan	1,510	2	11,349	—	—	11,351
Warrants exercised	61	—	—	—	—	—
Share-based compensation expense	—	—	9,910	—	—	9,910
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	—	—	(125,311)	—	—	(125,311)
Issuance of common stock for Symphony GenIsis acquisition	3,384	3	51,090	—	—	51,093
Balance at December 31, 2007	87,239	$ 87	$ 827,992	$ 538	$ (827,745)	$ 872
Comprehensive Loss:						
Net loss applicable to common stock	—	—	—	—	(11,963)	(11,963)
Change in unrealized gains	—	—	—	444	—	444
Comprehensive loss	—	—	—	—	—	(11,519)
Options exercised and employee stock purchase plan	1,510	2	12,550	—	—	12,552
Warrants exercised	3,423	3	160	—	—	163
Share-based compensation expense	—	—	15,063	—	—	15,063
Issuance of common stock to Genzyme Corporation	5,000	5	49,956	—	—	49,961
Balance at December 31, 2008	97,172	$ 97	$ 905,721	$ 982	$ (839,708)	$ 67,092

See accompanying notes.

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

	Years Ended December 31,		
	2008	2007	2006
Operating activities:			
Net loss	$ (11,963)	$ (10,994)	$ (45,903)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	2,868	2,667	3,854
Amortization of patents	1,610	1,623	1,633
Amortization of licenses	2,339	2,335	2,335
Amortization of discount on investments, net	(225)	(773)	(606)
Amortization of debt issuance costs	797	913	603
Share-based compensation expense	15,063	9,910	5,747
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc	—	(23,157)	(23,021)
Loss attributed to noncontrolling interest in Regulus Therapeutics Inc.	(4,734)	(629)	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	(2,103)	—	—
Gain from derivative instruments issued to Abbott Molecular Inc	(5,326)	—	—
(Gain) loss on investments, net	965	(3,510)	(2,263)
Loss on early retirement of debt	—	3,212	—
Non-cash losses related to patents and property, plant and equipment	1,877	896	2,410
Changes in operating assets and liabilities:			
Contracts receivable	1,238	(3,782)	1,523
Inventory	(1,323)	(1,956)	90
Other current and long-term assets	(2,657)	(494)	(796)
Accounts payable	962	(794)	1,214
Accrued compensation	(3,255)	4,239	2,516
Accrued liabilities	4,923	723	(2,135)
Deferred contract revenues	210,975	55,665	(426)
Net cash provided by (used in) operating activities	212,031	36,094	(53,225)
Investing activities:			
Purchase of short-term investments	(483,129)	(95,371)	(107,025)
Proceeds from the sale of short-term investments	265,951	119,956	72,575
Purchases of property, plant and equipment	(13,665)	(2,293)	(1,042)
Acquisition of licenses and other assets	(3,402)	(2,717)	(1,514)
Proceeds from the sale of strategic investments	—	5,181	4,397
Acquisition of Symphony GenIsis, Inc.	—	(80,400)	—
Net cash used in investing activities	(234,245)	(55,644)	(32,609)
Financing activities:			
Net proceeds from issuance of equity	12,714	11,351	86,364
Proceeds from issuance of convertible promissory note to GlaxoSmithKline	5,000	—	—
Proceeds from equipment financing arrangement	7,048	—	—
Proceeds from issuance of $2^5/_8$% convertible subordinated notes, net of issuance costs	—	157,056	—
Principal and redemption premium payment on prepayment of the $5^1/_2$% convertible subordinated notes	—	(127,021)	—
Principal payments on debt and capital lease obligations	(7,239)	(7,736)	(7,851)
Proceeds from stock purchase by Genzyme Corporation, net of fees	49,962	—	—
Proceeds from capital contributions to Ibis Biosciences, Inc.	40,000	—	—
Proceeds from capital contribution to Regulus Therapeutics Inc.	100	10,000	—
Proceeds from contribution to noncontrolling interest in Symphony GenIsis, Inc., net of fees	—	—	70,950
Net cash provided by financing activities	107,585	43,650	149,463
Net increase in cash and cash equivalents	85,371	24,100	63,629
Cash and cash equivalents at beginning of year	138,614	114,514	50,885
Cash and cash equivalents (including cash and cash equivalents classified as assets held for sale of $6.1 million, $0 and $0 at December 31, 2008, 2007 and 2006, respectively) at end of year	$ 223,985	$ 138,614	$ 114,514
Supplemental disclosures of cash flow information:			
Interest paid	$ 4,607	$ 6,212	$ 8,431
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ —	$ —	$ 18,590
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 2,873	$ 1,013	$ 979
Common stock issued for Symphony GenIsis, Inc. acquisition	$ —	$ 51,093	$ —
Acquisition of property, plant and equipment	$ —	$ —	$ 361

See accompanying notes

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd., Orasense, Ltd. and Symphony GenIsis, Inc. On September 27, 2007, we purchased all of the equity in Symphony GenIsis as more fully described in *Note 7—Collaborative Arrangements and Licensing Agreements*. On October 25, 2006, we dissolved the Orasense, Ltd. subsidiary.

In addition to our wholly owned subsidiaries, our consolidated financial statements include two variable interest entities, Ibis Biosciences, Inc. and Regulus Therapeutics Inc., for which we are the primary beneficiary as defined by Financial Accounting Standards Board Interpretation ("FIN") 46R (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB 51*. As a result of announcing the sale of Ibis to Abbott Molecular Inc., or AMI, in December 2008, we have presented Ibis' financial position and results of operations separately as discontinued operations in our consolidated financial statements in accordance with Statement of Financial Accounting Standards ("SFAS") 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*. We have reclassified amounts in the prior period financial statements to conform to the current period presentation. Until the acquisition of Symphony GenIsis, in September 2007, we identified Symphony GenIsis as a variable interest entity for which we were the primary beneficiary. The consolidated financial statements leading up to the acquisition date of Symphony GenIsis also include the financial condition and results of operations of Symphony GenIsis. We have eliminated all significant intercompany balances and transactions.

Organization and business activity

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

Basic net loss per share

We follow the provisions of SFAS 128, *Earnings per Share*. We compute basic net loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period. We compute diluted net loss per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period. Diluted common equivalent shares at December 31, 2008 consisted of 2.9 million shares issuable upon exercise of stock options and 1.5 million shares issuable upon exercise of warrants. The calculation excludes the $2^5/_8\%$ convertible subordinated notes, the convertible promissory note to GlaxoSmithKline, or GSK, and 3.1 million stock options because the effect on diluted earnings per share would be anti-dilutive. As we incurred a net loss for the years ended December 31, 2008, 2007 and 2006, we did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and we record contract revenue as we earn it based on the performance requirements of our collaborative research and development contracts. We recognize contract revenue for which no further performance obligations exist when we receive the payments and when we are reasonably certain we can collect the receivable. We record payments received in excess of amounts earned as deferred contract revenue. We expense research and development costs as incurred. For the years ended December 31, 2008, 2007 and 2006, research and development costs of approximately $45.0 million, $9.4 million, and $3.7 million, respectively, were related to collaborative research and development arrangements.

Revenue Recognition

We follow the provisions as set forth by Staff Accounting Bulletin ("SAB") 101, *"Revenue Recognition in Financial Statements,"* SAB 104, *"Revenue Recognition,"* and Financial Accounting Standards Board Emerging Issues Task Force ("EITF") 00-21, *"Accounting for Revenue Arrangements with Multiple Deliverables."*

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

Research and development revenue under collaborative agreements

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

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we have no future performance obligations related to the achievement of the milestone.

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that we had met the provisions in SAB 104 before we recognized the related revenue.

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

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing 5 million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represents value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement. See further discussion about our collaboration with Genzyme in *Note 7—Collaborative Arrangements and Licensing Agreements.*

Licensing and royalty revenue

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

Concentration of credit risk

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

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than ninety days from date of purchase. We classify our securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* We carry our available-for-sale securities at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include gross realized gains and losses in investment income. We use the specific identification method to determine the cost of securities sold.

We also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. 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 issuer, near term prospects of the issuer and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting according to Accounting Principles Board ("APB") 18, *The Equity Method of Accounting for Investments in Common Stock.* When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During 2008, we recognized a $965,000 loss on investments consisting of $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals Inc. and a $198,000 gain that we realized on our available-for-sale securities. See further discussion about our investment in OncoGenex in *Note 7—Collaborative Arrangements and Licensing Agreements.* During 2007, we sold the remainder of our equity securities of Alnylam Pharmaceuticals, Inc. that we owned resulting in a realized gain of $3.5 million, compared to a net gain on investments of $2.3 million during 2006. The net gain on investments during 2006 represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we owned, offset by a non-cash loss of $465,000 related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Limited, or ATL. We determined that there were no other-than-temporary declines in value of investments in 2007.

Inventory valuation

In accordance with SFAS 2, *Accounting for Research and Development Costs*, 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 and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-off for the years ended December 31, 2008, 2007 and 2006. Total inventory, which consisted of raw materials, was $2.7 million and $1.8 million as of December 31, 2008 and 2007, respectively.

Property, plant and equipment

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

	December 31,	
	2008	2007
Equipment and computer software	$ 30,328	$ 22,757
Leasehold improvements	17,705	12,081
Furniture and fixtures	1,775	1,522
	49,808	36,360
Less accumulated depreciation	(32,437)	(30,400)
	$ 17,371	$ 5,960

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

Equipment	5 years
Computer software	3 years
Furniture and fixtures	5 years

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

Licenses

We obtain licenses from third parties and capitalize the costs related to exclusive licenses. Our license from Idera Pharmaceuticals, Inc., formerly Hybridon, Inc., comprised the majority of the license balance as of December 31, 2008 and 2007. We amortize capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately 8 years and 15 years. The cost of our licenses at December 31, 2008 and 2007 was $36.0 million and $35.9 million, respectively. Accumulated amortization related to licenses was $19.2 million and $16.8 million at December 31, 2008 and 2007, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2009, 2010 and 2011 and $2.2 million for the years ending December 31, 2012 and 2013.

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs, if appropriate. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patents. The weighted average remaining life of issued patents was 3.4 years and 4.1 years at December 31, 2008 and 2007, respectively. In 2008, 2007 and 2006, we recorded a non-cash charge of $1.8 million, $887,000 and $2.8 million, respectively, which we included in research and development expenses and which was related to the assignment of patents to certain of our partners and the write-down of our patent costs to their estimated net realizable values.

Accumulated amortization related to patents was $11.8 million and $10.2 million at December 31, 2008 and 2007, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)
2009	$ 1.5
2010	$ 1.4
2011	$ 1.2
2012	$ 0.9
2013	$ 0.7

Fair value of financial instruments

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

Long-lived assets

We assess the value of our long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144 and we evaluate our long-lived assets for impairment on at least a quarterly basis. We recorded a charge of $1.9 million, $887,000 and $2.8 million for the years ended December 31, 2008, 2007 and 2006, respectively, primarily related to the assignment of patents to certain of our partners and the write-down of equipment and intangible assets to their estimated net realizable values.

Use of estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Consolidation of variable interest entities

We have implemented the provisions of FIN 46R, which addresses consolidation by business enterprises of 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. As of December 31, 2008, we had collaborative arrangements with nine entities that we considered to be variable interest entities ("VIE") under FIN 46R. For 2008, our consolidated financial statements include two variable interest entities, Ibis and Regulus, for which we were the primary beneficiary. For 2007, our consolidated financial statements included three variable interest entities, Ibis, Regulus and Symphony GenIsis, for which we were the primary beneficiary. For 2006, our consolidated financial statements included two variable interest entities, Ibis and Symphony GenIsis, for which we were the primary beneficiary. Until our acquisition of Symphony GenIsis in September 2007, we identified Symphony GenIsis as a variable interest entity that we consolidated.

Stock-based compensation

On January 1, 2006, we adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to the employee stock purchase plan based on estimated fair values. In March 2005, the SEC issued SAB 107 relating to SFAS 123R. We have applied the provisions of SAB 107 in our adoption of SFAS 123R.

SFAS 123R requires companies to estimate the fair value of stock-based payment awards on the date of grant using an option-pricing model. We recognize the value of the portion of the award that we ultimately expect to vest as expense over the requisite service period as stock-based compensation expense in our Consolidated Statements of Operations. For the years ended December 31, 2008, 2007 and 2006, our Consolidated Statements of Operations included compensation expense for stock-based payment awards granted prior to, but not yet vested as of December 31, 2005, based on the grant date fair value estimated in accordance with the pro forma provisions of SFAS 123 and compensation expense for the stock-based payment awards granted subsequent to December 31, 2005 based on the grant date fair value estimated in accordance with the provisions of SFAS 123R. We recognize compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. We reduce stock-based compensation expense for estimated forfeitures, which we estimate in accordance with SFAS 123R at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates.

As permitted by SFAS 123R, we utilize the Black-Scholes model as our method of valuation for stock-based awards granted. On the grant date, we use our stock price as well as assumptions regarding a number of highly complex and subjective variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although the estimated fair value of employee stock options is determined in accordance with SFAS 123R 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 record stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, at their fair value in accordance with the requirements of SFAS 123R, then periodically remeasure them in accordance with EITF 96-18, *Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, and recognize them over the service period.

See *Note 5—Stockholders' Equity* for additional information regarding our share-based compensation plans and the impact of adopting SFAS 123R.

Comprehensive loss

SFAS 130, *Reporting Comprehensive Income,* requires us to display comprehensive loss and its components as part of our full set of consolidated financial statements. The measurement and presentation of net loss did not change. Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that are excluded from net loss. Specifically, SFAS 130 requires unrealized holding gains and losses on our available-for-sale securities, which we report separately in stockholders' equity, to be included in accumulated other comprehensive loss. Comprehensive loss for the years ended December 31, 2008, 2007 and 2006 has been reflected in our Consolidated Statements of Stockholders' Equity.

Segment information

We operate in two separate segments; Drug Discovery and Development and Regulus. In accordance with SFAS 131, *Disclosure about Segments of an Enterprise and Related Information*, we provide segment financial information and results for our Drug Discovery and Development segment and our Regulus subsidiary based on the segregation of revenues and expenses we use for management's assessment of operating performance and operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment. Prior to announcing the sale of Ibis to AMI, we reported Ibis as a separate segment. In accordance with SFAS 144, we now report Ibis as discontinued operations for all periods presented in our consolidated financial statements.

Fair Value Measurements

In September 2006, the Financial Accounting Standards Board ("FASB") issued SFAS 157, *Fair Value Measurements*. SFAS 157 defines fair value, establishes a framework for measuring fair value in accordance with accounting principles generally accepted in the United States, and expands disclosures about fair value measurements. We adopted the provisions of SFAS 157 on January 1, 2008. Although the adoption of SFAS 157 did not impact our financial condition, results of operations, or cash flow, SFAS 157 requires us to provide additional disclosures as part of our financial statements.

SFAS 157 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions, which included the derivative instruments related to the subscription right and call option we granted to AMI. In June and December 2008, AMI exercised the subscription right and call option, respectively. As such, we recorded the resulting difference in fair value in discontinued operations.

We measure our assets and liabilities that SFAS 157 requires us to measure at fair value on a recurring basis using the following inputs in accordance with SFAS 157 at December 31, 2008 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents and short-term investments (1)	$ 471,460	$ 206,209	$ 265,251	$ —
Equity securities (2)	1,821	1,821	—	—
Total	$ 473,281	$ 208,030	$ 265,251	$ —

(1) Included in cash and cash equivalents, short-term investments and assets held for sale on our Consolidated Balance Sheet.

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

The following table presents a reconciliation of the liabilities measured at fair value on a recurring basis using significant unobservable inputs (Level 3) during 2008 (in thousands):

	Derivative Instruments
Balance at January 1, 2008	$ —
Issuance of derivative instruments	5,376(1)
Adjustment to fair value included in discontinued operations	(5,326)(2)
Exercise of subscription right	(50)(3)
Balance at December 31, 2008	$ —

(1) Represents the derivative instruments related to the subscription right and call option granted to AMI (see additional discussion in *Note 7—Collaborative Arrangements and Licensing Agreements*). We used a combination of two valuation models, a binomial lattice model and a Black-Scholes model, to derive the value of the derivative instruments.

(2) We revalued the subscription right and call option we granted to AMI until AMI exercised them in June and December 2008, respectively. During 2008, the adjustment to fair value resulted in a gain, which we included in discontinued operations.

(3) AMI exercised the subscription right on June 27, 2008 (see additional discussion in *Note 7—Collaborative Arrangements and Licensing Agreements*).

Additionally, in February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities*. This statement allows entities to account for most financial instruments at fair value rather than under other applicable GAAP, such as historical cost. SFAS 159 requires us to mark an asset or liability to fair value every reporting period with the gain or loss from a change in fair value recorded in the statement of operations. We adopted the provisions of SFAS 159 in the first quarter of 2008. SFAS 159 permits companies to make an election to carry certain eligible financial assets and liabilities at fair value. We have made the election not to measure any additional assets and liabilities at fair value other than our available-for-sale and equity securities that are revalued under SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities* and the derivative instruments outstanding in 2008 that we revalued under SFAS 133, *Accounting for Derivative Instruments and Hedging Activities*. Therefore, the adoption of SFAS 159 did not impact our results of operations, financial position or cash flows.

Income Taxes

In July 2006, the FASB issued Interpretation No. 48, *Accounting for Uncertainty in Income Taxes—An Interpretation of FASB Statement No. 109* ("FIN 48"), which clarifies the accounting for uncertainty in income taxes recognized in an entity's financial statements in accordance with SFAS No. 109, *Accounting for Income Taxes*, and prescribes a recognition threshold and measurement attributes for financial statement disclosure of tax positions an entity has taken or expects to take on a tax return. FIN 48 requires an entity to recognize the impact of an uncertain income tax position on the income tax return at the largest amount that the relevant taxing authority is more-likely-than-not sustain upon audit. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained. Additionally, FIN 48 provides guidance on derecognition, classification, interest and penalties, accounting in interim periods and disclosure. FIN 48 is effective for fiscal years beginning after December 15, 2006.

Impact of recently issued accounting standards

In December 2007, the FASB issued SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment to ARB No. 51*. This statement recharacterizes the accounting and reporting for minority interests as noncontrolling interests and classifies them as a component of equity. SFAS 160 applies to all entities that prepare consolidated financial statements, but will affect only those entities that have an outstanding noncontrolling interest in one or

more subsidiaries or that deconsolidate a subsidiary. This statement is effective for fiscal years beginning after December 15, 2008, and will be effective for our fiscal year 2009. We do not expect the adoption of SFAS 160 to have a material impact on our results of operations and financial position but the requirements of SFAS 160 will impact how we present noncontrolling interests in our consolidated financial statements. SFAS 160 requires that we apply the standard retrospectively to all periods we present.

In May 2008, the FASB issued Staff Position No. APB 14-1, *Accounting for Convertible Debt Instruments That May be Settled in Cash upon Conversion (Including Partial Cash Settlement)*, ("FSP No. APB 14-1"). This standard states that entities with convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) should separate the liability and equity components of the instruments in a manner that will reflect the entity's nonconvertible debt borrowing rate when entities recognize interest cost in subsequent periods. FSP No. APB 14-1 requires that an entity assign a value to the debt component equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in the entity recording the debt at a discount. The entity then must amortize the resulting debt discount over the expected life of the debt as additional non-cash interest expense. This standard is effective for fiscal years beginning on or after December 15, 2008 and will be effective for our fiscal year 2009. This standard requires entities to apply the standard retrospectively to all periods the entity presents. The adoption of FSP No. APB 14-1 will not impact our cash, cash equivalents and short-term investments but we anticipate that it will significantly increase the amount of interest expense that we record in our statement of operations due to the non-cash amortization of the debt discount. Additionally, we anticipate that the adoption of this standard will significantly decrease our debt balance as of December 31, 2008, with a corresponding increase to shareholders' equity.

In June 2008, the EITF issued EITF 07-05, *Determining Whether an Instrument (or Embedded Feature) Is Indexed to an Entity's Own Stock*. EITF 07-05 clarifies the determination of whether an instrument (or an embedded feature) is indexed to an entity's own stock, which would qualify as a scope exception under SFAS 133, *Accounting for Derivative Instruments and Hedging Activities*. EITF 07-05 is effective for financial statements issued for fiscal years beginning after December 15, 2008, and will be effective for our fiscal year 2009. EITF 07-05 does not permit early adoption for an existing instrument. We do not expect this new guidance to have a material impact on our consolidated financial statements.

2. Discontinued Operations

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

We reflect Ibis as a discontinued operation because Ibis meets the criteria for a component of an entity under SFAS 144. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. The components of discontinued operations for the periods presented are as follows (in thousands):

	Year Ended December 31,		
	2008	2007	2006
Revenue	$ 12,586	$ 11,277	$ 9,673
Total operating expenses	28,393	17,306	12,573
Loss from operations	(15,807)	(6,029)	(2,900)
Other income, net	5,317	—	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	2,103	—	—
Net loss from discontinued operations	$ (8,387)	$ (6,029)	$ (2,900)
Basic and diluted net loss per share from discontinued operations	$ (0.09)	$ (0.07)	$ (0.04)

We report the following assets and liabilities as assets and liabilities held for sale in the accompanying Consolidated Balance Sheets (in thousands):

	December 31, 2008	December 31, 2007
Cash and cash equivalents	$ 6,067	$ —
Contracts receivable	818	1,316
Inventories	1,422	1,055
Property, plant and equipment, net	2,792	1,171
Patents, net	2,001	1,329
Other assets	2,362	1,503
Assets held for sale	$ 15,462	$ 6,374
Accounts payable	2,632	1,939
Accrued compensation	371	1,703
Accrued liabilities	1,982	1,581
Notes payable	585	—
Deferred contract revenue	2,300	1,670
Liabilities held for sale	$ 7,870	$ 6,893
Noncontrolling interest in Ibis Biosciences, Inc. — Held for sale	$ 32,419	$ —

As permitted by SFAS 95, *Statement of Cash Flows*, we have not separately classified cash flows from discontinued operations in our Consolidated Statement of Cash Flows.

3. Investments

As of December 31, 2008, our excess cash is primarily invested in commercial paper and debt instruments of financial institutions, corporations and U.S. government agencies with strong credit ratings. 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, 2008:

One year or less	87%
After one year but within five years	13%
Total	100%

We have an ownership interest of less than 20% in each of five private companies and three public companies we conduct business with and account for securities in the privately-held companies under the cost method of accounting according to APB 18, *The Equity Method of Accounting for Investments in Common Stock.* The companies are ATL, iCo Therapeutics Inc. and OncoGenex, which are publicly-traded, and Santaris Pharma A/S, formerly Pantheco A/S, Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard Pharmaceuticals, Inc., which are privately-held. During 2008, we recognized a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex. See further discussion about our investment in OncoGenex in *Note 7—Collaborative Arrangements and Licensing Agreements.* See *Note 1—Organization and Significant Accounting Policies* for a discussion of impairment losses incurred in 2008 and 2006.

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

December 31, 2008	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term Investments:					
Corporate debt securities	$ 111,569	$ 150	$ (307)	$ —	$ 111,412
Debt securities issued by U.S. government agencies	124,051	882	(19)	—	124,914
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	—	275
Total short-term portion	235,895	1,032	(326)	—	236,601
Corporate debt securities	13,608	5	(371)	—	13,242
Debt securities issued by U.S. government agencies	23,199	56	(18)	—	23,237
Total long-term portion	36,807	61	(389)	—	36,479
Subtotal	$ 272,702	$ 1,093	$ (715)	$ —	$ 273,080
Equity securities:					
Short-term portion	$ 2,380	$ 604	$ —	$ (1,163)	$ 1,821
Long-term portion	625	—	—	—	625
Subtotal	$ 3,005	$ 604	$ —	$ (1,163)	$ 2,446
	$ 275,707	$ 1,697	$ (715)	$ (1,163)	$ 275,526

December 31, 2007	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term Investments:				
Corporate debt securities	$ 48,827	$ 8	$ (4)	$ 48,831
Debt securities issued by U.S. government agencies	2,999	—	—	2,999
Debt securities issued by states of the United States and political subdivisions of the states	3,275	—	—	3,275
Subtotal	$ 55,101	$ 8	$ (4)	$ 55,105
Equity securities:				
Short-term portion	$ 880	$ 534	$ —	$ 1,414
Long-term portion	2,125	—	—	2,125
Subtotal	$ 3,005	$ 534	$ —	$ 3,539
	$ 58,106	$ 542	$ (4)	$ 58,644

Investments we consider to be temporarily impaired at December 31, 2008 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	33	$ 66,338	$ (678)
Debt securities issued by U.S. government agencies	4	13,648	(37)
Total temporarily impaired securities	37	$ 79,986	$ (715)

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 intend to hold these securities to maturity and anticipate full recovery of amortized cost with respect to these securities at maturity.

4. Long-Term Obligations and Commitments

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

	December 31, 2008	December 31, 2007
Standard operating debt	$ —	$ 7,238
GlaxoSmithKline convertible promissory note, including accrued interest	5,179	—
2 5/8% convertible subordinated notes	162,500	162,500
Equipment financing arrangement	6,463	—
Other obligations	361	362
Total	$ 174,503	$ 170,100
Less: current portion	(2,065)	(7,238)
Total Long-Term Obligations	$ 172,438	$ 162,862

Standard Operating Debt

In December 2003, we obtained a $32.0 million term loan from Silicon Valley Bank, which was scheduled to mature in December 2008. In September 2008, we fully paid the remaining principal balance of $1.8 million plus accrued but unpaid interest.

GlaxoSmithKline Convertible Promissory Note

In connection with the strategic alliance with GlaxoSmithKline ("GSK") in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25% at December 31, 2008. At December 31, 2008, the principal and accrued interest on the note was $5 million and $179,000, respectively. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock. We did not include the effect of the conversion of the note into our common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

Convertible Subordinated Notes

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

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

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

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing. Under the loan agreement, we may borrow up to $10 million in principal to finance the purchase of equipment. Each loan under the loan agreement will have a term of approximately 3 years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the 3 year interest rate swap at the time we make each draw down plus 4%, which was 7.22% at December 31, 2008. We are using the equipment purchased under the loan agreement as collateral. The carrying balance under this loan agreement at December 31, 2008 was $6.5 million. Under the same loan agreement, Ibis borrowed $600,000 in principal to finance the purchase of equipment. The carrying balance under this loan agreement at December 31, 2008 was $585,000 and was included in the liabilities held for sale line item within the accompanying Consolidated Balance Sheet.

Other Obligations

As of December 31, 2008 and 2007, we had approximately $361,000 and $362,000, respectively, under various contractual obligations.

Annual debt and other obligation maturities at December 31, 2008 are as follows (in thousands):

2009	$ 2,065
2010	2,220
2011	7,359
2012	1
2013	2
Thereafter	162,856
Total	$ 174,503

We lease certain office equipment and office and lab space under non-cancelable operating leases with terms through September 2020. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire in 2010, 2011 and 2012. The leases that expire in 2010 and 2011 have two five-year options to extend the lease while the lease that expires in 2012 has one five-year option to extend the lease. In connection with the sale of our 28,704 square foot manufacturing facility in 2005, we leased back the facility for an initial term of fifteen years with an initial rent of $2.60 per rentable square foot. Under the terms of the lease, the monthly rent will increase five percent every two years. The lease expires in 2020 and provides us an option to extend the lease for up to two five-year periods. In connection with the lease, we executed a stand by letter of credit for $500,000.

Annual future minimum payments under operating leases as of December 31, 2008 are as follows (in thousands):

	Operating Leases
2009	$ 3,119
2010	2,675
2011	1,802
2012	1,232
2013	1,052
Thereafter	7,809
Total minimum payments	$ 17,689

Rent expense for the years ended December 31, 2008, 2007, and 2006 was $3.8 million, $3.4 million, and $3.2 million, respectively. In connection with the sales leaseback of our manufacturing facility, we recognize rent expense on a straight line basis over the lease term resulting in a deferred rent balance of $469,000 and $354,000 at December 31, 2008 and 2007, respectively, which we include in liabilities on our balance sheet.

5. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2008 and 2007, there were no shares of Isis' Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible Exchangeable 5% Preferred Stock outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series C Junior Participating Preferred Stock

In December 2000, we adopted a Preferred Share Purchase Rights Plan ("Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right ("Right") for each outstanding share of our common stock, par value $0.001 per share ("Common Shares"), held of record at the close of business on January 10, 2001, and on each subsequently issued share of our common stock. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20% or more of our common stock, the Rights permit the holders (except the 20% holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a Common Share. Certain conditions allow our Board of Directors to redeem the Rights in whole, but not in part, at a price of $0.001 per Right. As of December 31, 2008 and 2007, there were no shares of the Preferred Shares outstanding.

Common Stock

In May 2006, after receiving approval from our stockholders, we amended our Restated Certificate of Incorporation to increase the authorized number of shares of our common stock from 100,000,000 shares to 200,000,000 shares. At December 31, 2008 and 2007, we had 200,000,000 shares of common stock authorized, of which 97,172,380 and 87,239,423 were issued and outstanding, respectively. As of December 31, 2008, total common shares reserved for future issuance were approximately 20,906,345.

We issued 1.5 million shares of common stock for stock option exercises and the Employee Stock Purchase Plan ("ESPP") purchases for each of the years ending December 31, 2008 and 2007. We received net proceeds from these transactions of $12.6 million and $11.4 million in 2008 and 2007, respectively.

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

In September 2007, we purchased the equity of Symphony GenIsis for $120.0 million, $80.4 million in cash and the remaining amount in approximately 3.4 million shares of our common stock.

Stock Option Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 16,700,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At December 31, 2008, a total of 5,640,611 options were outstanding, options to purchase 3,354,188 shares were exercisable, and 3,679,617 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which, as amended, provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expired on December 31, 2008. At December 31, 2008, a total of 3,151,217 options were outstanding, 1,199,591 shares were exercisable, and 277,029 shares were available for future grant under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

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

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

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

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"). In May 2006, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance under the 2002 Plan from 600,000 shares to 850,000 shares. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2008, a total of 524,000 options were outstanding, 322,750 of the shares issued under the 2002 Plan were exercisable and 213,000 shares were available for future grant.

Employee Stock Purchase Plan

In 2000, our Board of Directors adopted, and the stockholders subsequently approved, the 2000 ESPP and we reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 200,000 shares of common stock for the ESPP, resulting in a total of 1.8 million shares authorized in the plan as of December 31, 2008. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the purchase period or the end of each six-month purchase period. During 2008, employees purchased and we issued to employees 147,148 shares under the ESPP at prices ranging from $8.30 to $11.80 per share. At December 31, 2008, 190,976 shares were available for purchase under the ESPP.

Stock Option Activity and Stock-Based Compensation Expense

The following table summarizes stock option activity for the year ended December 31, 2008 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2007	8,184	$ 8.50		
Granted	2,858	$ 15.32		
Exercised	(1,363)	$ 8.13		
Cancelled/forfeited/ expired	(363)	$ 12.50		
Outstanding at December 31, 2008	9,316	$ 10.49	3.93	$ 39,457
Exercisable at December 31, 2008	4,877	$ 8.19	3.13	$ 30,483

The following table summarizes information concerning outstanding and exercisable options as of December 31, 2008 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Term	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$2.96–$5.17	237	4.70	$ 4.49	208	$ 4.51
$5.24–$5.25	1,006	3.35	$ 5.25	663	$ 5.25
$5.35–$6.81	1,507	3.29	$ 6.27	1,415	$ 6.30
$6.81–$8.15	992	2.38	$ 7.08	871	$ 7.03
$8.25–$10.77	877	3.46	$ 9.66	604	$ 9.59
$10.82–$11.12	1,493	4.03	$ 11.12	701	$ 11.11
$11.13–$15.15	672	5.14	$ 13.31	149	$ 12.59
$15.38–$15.38	1,583	5.30	$ 15.38	1	$ 15.38
$15.40–$22.19	945	4.18	$ 17.38	261	$ 18.85
$22.83–$22.83	4	2.92	$ 22.83	4	$ 22.83
	9,316	3.93	$ 10.49	4,877	$ 8.19

The weighted-average estimated fair values of options granted were $7.44, $6.19 and $3.44 for the years ended December 31, 2008, 2007 and 2006, respectively. The total intrinsic value of options exercised during the years ended December 31, 2008, 2007 and 2006 were $11.2 million, $9.5 million and $6.6 million, respectively, which we determined as of the date of exercise. The amounts of cash received from the exercise of stock options were $11.1 million, $10.3 million and $10.9 million for the years ended December 31, 2008, 2007 and 2006, respectively. For the year ended December 31, 2008, the weighted-average fair value of options exercised was $16.34. As of December 31, 2008, total unrecognized compensation cost related to non-vested stock-based compensation plans was $14.3 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.3 years.

Stock-based Valuation and Compensation Expense Information under SFAS 123R

Impact of the Adoption of SFAS 123R

The following table summarizes stock-based compensation expense related to employee and non-employee stock options and the employee stock purchase plan under SFAS 123R for the year ended December 31, 2008, 2007 and 2006 (in thousands, except per share data), which was allocated as follows:

	Year Ended December 31,		
	2008	2007	2006
Research and development	$ 10,578	$ 6,745	$ 3,794
General and administrative	2,708	1,553	969
Non-cash compensation expense related to stock options included in continuing operations	13,286	8,298	4,763
Non-cash compensation expense related to stock options included in discontinued operations	1,777	1,612	984
Total	$ 15,063	$ 9,910	$ 5,747
Stock-based compensation expense, per share:			
Basic and diluted net loss per share included in continuing operations	$ 0.14	$ 0.10	$ 0.07
Basic and diluted net loss per share included in discontinued operations	0.02	0.02	0.01
Total	$ 0.16	$ 0.12	$ 0.08

For Regulus, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. Regulus records the expenses associated with these options on its books. Since we are consolidating the financial results of Regulus, we included $2.0 million and $412,000 of non-cash stock based compensation expense associated with these options for the years ended 2008 and 2007, respectively, in our consolidated expenses.

Determining Fair Value

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

We estimated the fair value of each stock option grant and the ESPP purchase rights on the date of grant using the Black-Scholes model with the following weighted-average assumptions (annualized percentages), which vary based on type of plan, for the years ended December 31, 2008, 2007 and 2006:

Employee Stock Options:

	December 31,		
	2008	2007	2006
Risk-free interest rate	3.1%	4.6%	4.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	55.2%	63.1%	68.6%
Expected life	4.6 years	4.6 years	4.6 years

Board of Director Stock Options:

	December 31,		
	2008	2007	2006
Risk-free interest rate	3.8%	4.9%	5.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	62.2%	65.5%	85.2%
Expected life	7.6 years	7.4 years	7.0 years

ESPP:

	December 31,		
	2008	2007	2006
Risk-free interest rate	2.8%	5.1%	4.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	61.4%	51.1%	49.9%
Expected life	6 months	6 months	6 months

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

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

Volatility. We used a weighted average of the historical stock price volatility of our stock for the Black-Scholes model consistent with SFAS 123R. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options granted represents the period of time that we expect them to be outstanding. For the 2002 Plan, we estimated the expected term of options granted based on historical exercise patterns. For the 1989 Plan and 2000 Plan, we estimated the expected term of options granted subsequent to January 1, 2008, based on historical exercise patterns. The expected term for stock options granted prior to January 1, 2008 was a derived output of the simplified method, as allowed under SAB 107.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. Forfeitures are estimated in accordance with SFAS 123R at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

Warrants

In August 2005, we raised $51.0 million in a private placement of 12 million shares of our common stock. Investors in the financing also received five-year warrants to purchase an aggregate of approximately 3 million shares of common stock at an exercise price of $5.2395 per share. Investors in the financing had exercised all of the warrants as of December 31, 2008.

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. These warrants expire on April 7, 2011 and can be settled with unregistered shares of our common stock. As of December 31, 2008, 479,401 shares of common stock under the warrants remained outstanding. If we enter into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than us, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares of common stock of the surviving entity as follows:

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

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

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

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

We evaluated the provisions of the Registration Rights Agreement and the Warrant Purchase Agreement under EITF 00-19, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,* and determined that the criteria for equity classification were met; therefore, the warrants were accounted for as part of stockholders' equity.

6. Income Taxes

In July 2006, the FASB issued Interpretation No. 48, *Accounting for Uncertainty in Income Taxes—An Interpretation of FASB Statement No. 109* ("FIN 48"), which clarifies the accounting for uncertainty in income taxes recognized in an entity's financial statements in accordance with SFAS No. 109, *Accounting for Income Taxes*, and prescribes a recognition threshold and measurement attributes for financial statement disclosure of tax positions taken or expected to be taken on a tax return. FIN 48 requires an entity to recognize the impact of an uncertain income tax position on the income tax return at the largest amount that the relevant taxing authority is more-likely-than-not sustain upon audit. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained.

Additionally, FIN 48 provides guidance on derecognition, classification, interest and penalties, accounting in interim periods and disclosure. FIN 48 is effective for fiscal years beginning after December 15, 2006.

We adopted the provisions of FIN 48 on January 1, 2007, and have commenced analyzing filing positions in all of the federal and state jurisdictions where we are required to file income tax returns, as well as all open tax years in these jurisdictions. As a result, we have recorded no additional tax liability. The total amount of unrecognized tax benefits as of January 1, 2007 was $0. We have not yet completed an analysis of our deferred tax assets for net operating losses of $207.4 million and research and development credits of $46.5 million generated from our inception until December 31, 2008. Due to uncertainties surrounding our ability to generate future taxable income to realize these assets, we have established a full valuation to offset our net deferred tax asset. Pursuant to Internal Revenue Code Sections 382 and 383, annual usage of our net operating loss and credit carryforwards to offset future taxable income may be limited due to changes in ownership of more than 50%. We have not yet determined whether such an ownership change has occurred. As such, these amounts and the offsetting valuation allowance have been removed from our deferred tax assets until we complete a Section 382 analysis. However, we plan to complete a Section 382 analysis in 2009 regarding the limitation of our net operating losses and research and development credits. When this project is completed, we plan to update the unrecognized tax benefits under FIN 48. Therefore, the unrecognized tax benefits will change within 12 months of this reporting date. At this time, we cannot estimate how much the unrecognized tax benefits may change. Due to the existence of the 100% valuation allowance, future changes in our unrecognized tax benefits will not impact our effective tax rate or our consolidated financial statements.

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

Our practice is to recognize interest and/or penalties related to income tax matters in income tax expense. Upon adoption of FIN 48 on January 1, 2007, we did not record any interest or penalties. During the year ended December 31, 2008, we did not recognize any interest or penalties.

Our deferred tax liabilities were $6.6 million and $6.3 million at December 31, 2008 and 2007, respectively. As discussed above, as of January 1, 2007, we have removed our net operating losses and research and development credits from our deferred tax assets and the offsetting valuation allowance at December 31, 2008 until we complete a Section 382 analysis. Our remaining deferred tax assets at December 31, 2008 were $61.1 million and our deferred tax assets at December 31, 2007 were $50.8 million. We have established full valuation allowance of $54.5 million and $44.5 million to offset the net deferred tax assets as of December 31, 2008 and 2007, respectively, as realization of these assets is uncertain.

As a result of certain realization requirements of SFAS 123(R), the deferred tax assets and liabilities shown above do not include certain deferred tax assets at December 31, 2008 and 2007 that arose directly from (or the use of which was postponed by) tax deductions related to equity compensation in excess of compensation recognized for financial reporting. Those deferred tax assets include non-qualified stock options and incentive stock options issued by us. Equity will be increased by $24.8 million if and when such deferred tax assets are ultimately realized. We use tax return ordering for purposes of determining when excess tax benefits have been realized.

At December 31, 2008, we had federal, California and foreign tax net operating loss carryforwards of approximately $591.1 million, $180.6 million and $1.1 million, respectively. The Federal and California tax loss carryforwards will continue to expire in 2008 and 2013, unless previously utilized. We also had federal and California research and development tax credit carryforwards of approximately $31.3 million and $22.2 million, respectively. The Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless utilized. The California research and development tax credit carryforwards are available indefinitely. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years' California loss carryforwards. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a research relationship. The transaction, which closed in June 2008, included a $175 million licensing fee, a $150 million equity investment in us where we issued Genzyme five million shares of our common stock at $30 per share, over $1.5 billion in potential milestone payments and a share of profits on mipomersen and follow-on drugs ranging from 30 to 50% of all commercial sales. Under this alliance, Genzyme is responsible for the commercialization of mipomersen. We will contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable. As part of our alliance, Genzyme is our preferred partner for the development and commercialization of antisense drugs for neurodegenerative and certain rare diseases.

Genzyme has agreed that it will not sell the Isis stock that it purchased in February 2008 until the earlier of four years from the date of our mipomersen License and Co-Development Agreement, the first commercial sale of mipomersen or the termination of our mipomersen License and Co-Development Agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen License and Co-Development Agreement or the date Genzyme holds less than 2% of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

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

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

In September 2007, we entered into a collaboration with Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMJP worldwide development and commercialization rights to two of our diabetes programs. Additionally, OMJP is providing funding to us to support a focused research program in metabolic disease. Under the terms of the agreement, OMJP paid us a $45 million upfront licensing fee, which we are amortizing over the two year period of our performance obligation based on the research plan included in the agreement. OMJP is also providing us with research and development funding over the two year period of the collaboration. In addition to the licensing fee, we will also receive over $225 million in milestone payments upon successful development and regulatory approvals of antisense drugs that target GCGR and GCCR, as well as royalties on sales. We will also receive milestone payments and royalties on the successful development and regulatory approvals of additional drugs discovered as part of the collaboration.

In September 2007, we initiated the Phase 1 clinical trial in our OMJP-GCGR program for which we earned the first development milestone payment of $5 million. Since we achieved the milestone before we finalized the contract, from an accounting perspective, we are treating the milestone payment as part of the upfront licensing fees and are amortizing the $5 million over the two year period of our performance obligation. During 2008 and 2007, we recognized revenue of $31.9 million and $13.2 million, respectively, related to the upfront licensing fee, the milestone payment and the research and development funding, which represented 30% and 23% of our total revenue for those years. Our balance sheets at December 31, 2008 and 2007 included deferred revenue of $16.7 million and $41.7 million, respectively, related to the upfront licensing fee and milestone payment.

Bristol-Myers Squibb Company

In May 2007, we entered into a collaboration agreement with Bristol-Myers Squibb Company, or BMS, to discover, develop and commercialize novel antisense drugs targeting PCSK9. Under the terms of the agreement, we received a $15 million upfront licensing fee and are amortizing this amount over the three year period of our performance obligation based on the research plan included in the agreement. BMS will also provide us with at least $9 million in research funding over an initial period of three years. In April 2008, BMS designated the first development candidate resulting from the collaboration for which we earned a $2 million milestone payment. We will also receive up to $166 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestone payments associated with development of follow-on compounds. BMS will also pay us royalties on sales of products resulting from the collaboration. During 2008 and 2007, we recognized revenue of $12.0 million and $5.2 million related to the upfront licensing fee, milestone payment and the research funding, which represented 11% and 9% of our total revenue for those years. Our balance sheets at December 31, 2008 and 2007 included deferred revenue of $6.7 million and $11.7 million, respectively, related to the upfront licensing fee.

Pfizer Inc.

In May 2005, we entered into a multi-year drug discovery collaboration with Pfizer to identify second-generation antisense drugs for the treatment of ophthalmic disease. In addition to the collaboration agreement, we have entered into a target validation agreement with Pfizer. Under the terms of the collaboration agreement, we received an upfront technology access fee of $1 million and amortized this amount over the one year period of our performance, which ended in April 2006, based on the research plan included in the agreement. There were no changes in our period of performance. As of December 31, 2008, we earned milestone payments totaling $1.2 million under the collaboration agreement. In 2008, this collaboration ended in accordance with its terms. During 2008, 2007 and 2006, we earned revenue of $360,000, $445,000 and $547,000, respectively. Our balance sheets as of December 31, 2008 and 2007 included deferred revenue of $540,000 and $900,000, respectively, related to our target validation agreement with Pfizer.

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly, which included a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases. Subsequently, we extended the research collaboration with Lilly to focus on a select number of targets. As part of the collaboration, Lilly licensed LY2181308, our antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. As of December 31, 2008, we had earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. Lilly is responsible for the preclinical and clinical development of LY2181308 and LY2275796 and we have no performance obligations for LY2275796. Our balance sheets as of December 31, 2008 and 2007 included deferred revenue of $0 and $156,000, respectively, related to a prepayment that Lilly made to us for active pharmaceutical ingredient. We will receive additional milestone payments aggregating up to $25 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and in addition, royalties on future product sales of these drugs.

During 2008, we earned revenue from our relationship with Lilly totaling $156,000, compared to $402,000 and $1.2 million in 2007 and 2006, respectively.

Merck & Co., Inc.

In June 1998, we entered into a multi-year research collaboration and license agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a drug discovered in this collaboration into Phase 1 clinical trials for which we received a $1 million milestone payment. In addition to the milestone payment we received, Merck will pay us aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales. We recently removed the Merck drug from our pipeline because we have been unable to verify the development status of the drug with Merck. During 2008 and 2007, we did not recognize any revenue from our relationship with Merck, compared to $1.1 million in 2006, which is made up of the $1 million milestone payment and $60,000 pursuant to a non-exclusive license agreement.

Drug Discovery and Development Satellite Company Collaborations

Achaogen, Inc.

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

Altair Therapeutics Inc.

In October 2007, we licensed AIR645 to Altair, a venture capital-funded biotechnology company focusing on the discovery, development and commercialization of our antisense drugs to treat asthma and other respiratory conditions. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an inhaled inhibitor of the IL-4 and IL-13 signaling pathways for the treatment of asthma. Altair is solely responsible for the continued development of AIR645. At December 31, 2008 and 2007, we owned 18% of Altair in the form of preferred stock. At the time of receipt, we have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. In addition to the preferred stock, we will receive additional license fees and royalties if AIR645 and other drugs arising out of the research collaboration progress. During 2008 and 2007, we recognized revenue of $207,000 and $494,000, respectively, from our relationship with Altair, which does not include any revenue from the equity we received from Altair.

Antisense Therapeutics Limited

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

In addition to ATL/TV1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we extended for an additional two years in January 2007. ATL pays us cash for access to our antisense expertise and for research and manufacturing services we may provide to ATL during the collaboration. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, we received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering, representing an initial ownership percentage of approximately 14%. The initial ATL common stock we received had a value of $2.8 million, and we recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in our period of performance. Our Consolidated Balance Sheets at December 31, 2008 and 2007 included deferred revenue of $232,000 and $250,000, respectively, related to our agreements with ATL. During 2008, we recorded revenue of $1.6 million related to this collaboration compared to $80,000 and $652,000 for 2007 and 2006, respectively. At December 31, 2008 and 2007, our ownership percentage in ATL, including 10.3 million shares we purchased subsequent to shares we acquired in ATL's initial public offering, was less than 10% of ATL's equity. Our balance sheets at December 31, 2008 and 2007 included a short-term investment at fair market value of $1.1 million and $1.4 million, respectively, related to this equity investment.

Atlantic Pharmaceuticals Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based company that gastrointestinal drug developers founded in 2006 to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Pharmaceuticals plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. At the time of receipt, we have recognized a valuation allowance of $2 million to offset this asset as realization of this asset is uncertain. At December 31, 2008 and 2007, we owned approximately 13% of Atlantic Pharmaceuticals' equity. In addition, assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Pharmaceuticals meets specific development milestones, at Atlantic Pharmaceuticals' request, we will attempt to identify a second-generation lead drug candidate for Atlantic Pharmaceuticals. Atlantic Pharmaceuticals may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen, and, if selected, the second-generation lead drug candidate. During 2008 and 2007, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals because we do not recognize revenue when we receive equity in private companies.

Excaliard Pharmaceuticals, Inc.

In November 2007, we entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring. We have granted Excaliard an exclusive worldwide license for the development and commercialization of certain antisense drugs. Excaliard made an upfront payment to us in the form of equity and paid us $1 million in cash for the licensing of a particular gene target. At the time of receipt, we have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. At December 31, 2008 and 2007, we owned less than 10% of Excaliard's equity and we have no remaining performance obligations. In addition, assuming Excaliard successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $8.5 million for the achievement of key clinical and regulatory milestones, and royalties on antisense drugs Excaliard develops, as well as a portion of the fees Excaliard receives if it licenses the drugs. Our balance sheets at December 31, 2008 and 2007 included deferred revenue of $74,000 and $0, respectively, related to our agreements with Excaliard. During 2008 and 2007, we recognized revenue of $384,000 and $1 million, respectively, which does not include any revenue from the equity we received from Excaliard.

iCo Therapeutics Inc.

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

Over the course of our relationship with iCo, which became a publicly traded company on the Canadian Stock Exchange in 2008, they have paid us in a combination of cash and equity instruments, which included common stock and convertible notes. As a result of the equity instruments we received, on December 31, 2008, we owned less than 10% of iCo's equity, compared to approximately 10% at December 31, 2007. Our balance sheet at December 31, 2008 included a short-term investment at fair market value of $369,000 related to this equity investment. In February 2009, iCo completed a CAD$ 1.3 million financing to fund the completion of its Phase 1 clinical study of iCo-007. We participated in the financing and as a result our ownership in iCo is now approximately 14%. During 2008, we recognized revenue of $7,000 from our relationship with iCo, compared to $550,000 for 2006. During 2007, we did not recognize any revenue from our relationship with iCo.

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement with OncoGenex. Under the amended agreement, OncoGenex will independently develop and is responsible for all development costs and activities for OGX-011. We will receive royalties for OGX-011 ranging from 5.5% to 7% of net sales. In addition, OncoGenex will pay us 30% of the upfront fees and milestone payments that OncoGenex receives if OncoGenex licenses OGX-011 prior to initiation of registration trials, 25% if OncoGenex licenses OGX-011 before 20% of patients have been enrolled in a registration trial, 20% if OncoGenex licenses OGX-011 prior to marketing approval and 15% thereafter. In August 2003, the companies entered into a collaboration and license agreement for the development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427, which targets Hsp27. OncoGenex paid us an upfront fee of $750,000 with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-427.

During 2008, we did not recognize any revenue from our relationship with OncoGenex, compared to $4,000 and $1.2 million for 2007 and 2006, respectively. In August 2008, OncoGenex completed a reverse takeover of Sonus Pharmaceuticals, a publicly traded company, and became a subsidiary of Sonus, which was renamed OncoGenex Pharmaceuticals, Inc. As a result of this transaction, our shares of OncoGenex preferred stock converted into 122,485 shares of OncoGenex common stock, which is traded on the Nasdaq Capital Market. The carrying value of our equity investment in OncoGenex has been negatively affected by the unusually poor conditions of the financial markets recently. As a result, we recognized a $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex. Our balance sheets at December 31, 2008 and 2007 included a short-term investment at fair market value of $337,000 and $1.5 million, respectively, related to this equity investment. As of December 31, 2008 and 2007, our ownership interest in OncoGenex was less than 10%.

Novosom AG

In August 2008, we granted Novosom an exclusive, worldwide license to access certain antisense inhibitors targeting CD40 mRNA for a number of indications. Novosom plans to target CD40, a well established target for both inflammatory diseases and autoimmune diseases, for indications such as Crohn's disease, organ transplant or rheumatoid arthritis. In exchange for the exclusive, worldwide license, Novosom paid us an upfront payment. In addition, assuming Novosom successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $6 million for the achievement of key clinical and regulatory milestones. We will also receive royalties on sales of these antisense drugs Novosom develops. Furthermore, if Novosom sublicenses an antisense drug using our technology, we may be entitled to a portion of the consideration Novosom receives. We have no significant remaining obligations to perform under this agreement. During 2008, we recognized $375,000 in revenue from our relationship with Novosom

Technology Development Satellite Company Collaborations

Archemix Corp.

In August 2007, we and Archemix entered into a strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to our technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than targeting mRNA. Through this licensing partnership, we are providing access to our oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs based on Archemix's technology. In November 2007, we received a $250,000 milestone

payment from Archemix associated with the initiation of Phase 2a trials of their aptamer drug. We will receive a portion of any sublicensing fees Archemix generates as well as milestone payments and royalties on Archemix' drugs that use our technology. During 2008, we did not recognize any revenue from our relationship with Archemix, compared to $250,000 in 2007.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, the potential milestone payments from Alnylam total $3.4 million, which Alnylam will pay to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of December 31, 2008, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery. As of December 31, 2008, we have earned a total of $36.1 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners.

During 2007, 2006 and 2005, we sold our holdings of Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2008, we no longer own any shares of Alnylam. During 2008, 2007 and 2006, we generated revenue from our relationship with Alnylam totaling $4.6 million, $26.5 million and $750,000, respectively, representing 4%, 45% and 5%, respectively, of our total revenue for those years.

Ercole Biotech, Inc.

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

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

In March 2008, AVI BioPharma, Inc. acquired Ercole's rights and obligations under the collaboration agreement. As a result of our collaboration agreement with Ercole, as part of the acquisition, we received a warrant to purchase 238,228 shares of AVI's common stock at an exercise price of $0.1679 per share, and a warrant to purchase 207,757 shares of AVI's common stock at an exercise price of $3.61 per share. During 2008, 2007 and 2006, we did not recognize any revenue from our relationship with Ercole.

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1998 and September 2000, we entered into license agreements with Santaris, formerly Pantheco. Under the terms of the license agreements, which the companies amended and restated in May 2003, we licensed our novel antisense chemistry, Peptide Nucleic Acid to Santaris on a limited exclusive basis to develop products. As part of our original license agreements with Pantheco, we received shares of Pantheco stock. Our ownership interest in Santaris, which was formed in the merger of Pantheco and Cureon A/S, was less than 10% at December 31, 2008 and 2007. During 2008, 2007 and 2006, we did not recognize any revenue from our relationship with Santaris.

External Project Funding

CHDI, Inc.

In November 2007, we entered into an agreement with CHDI, which provides us with up to $9.9 million in funding for the discovery and development of an antisense drug for the treatment of Huntington's Disease. CHDI's funding builds upon an earlier successful collaboration between us and CHDI, in which CHDI funded proof-of-concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's Disease. During 2008, 2007 and 2006, we recognized revenue of $2.7 million, $329,000 and $70,000, respectively, from our relationship with CHDI.

Symphony GenIsis, Inc.

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

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of our common stock at an exercise price of $8.93 per share, a 25% premium over our 60-day average trading price at the time of the issuance, which was $7.14. As of December 31, 2008, warrants to purchase 479,401 shares remained outstanding. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, we paid structuring and legal fees of $4.1 million.

In September 2007, we exercised our option and purchased the equity of Symphony GenIsis for $120 million, $80.4 million in cash and the remaining amount in approximately 3.4 million shares of our common stock. Subsequent to the acquisition of Symphony GenIsis, we granted OMJP, as part of the collaboration agreement with them, worldwide development and commercialization rights to the two diabetes programs previously licensed to Symphony GenIsis, plus up to four additional antisense drugs. In addition, we reacquired full ownership of mipomersen, our cholesterol-lowering drug targeting apoB-100, which we licensed to Genzyme in January 2008. The $125.3 million on our Consolidated Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis represents a deemed dividend to the previous owners of Symphony GenIsis, a portion of which was non-cash. A portion of the $125.3 million reflects the significant increase in our stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts our net loss applicable to common stock and our net loss per share applicable to common stock calculations for 2007 and does not affect our net loss from continuing operations.

Korea Institute of Toxicology

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

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

In October 2005, we entered a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs in the areas of ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration. The researchers from the Ludwig Institute and Center for Neurological Studies, through funding from the ALS Association and the Muscular Dystrophy Association, are conducting IND-enabling preclinical studies of ISIS-SOD1$_{Rx}$. Except for the funding provided by the ALS Association and the Muscular Dystrophy Association, we control and are responsible for funding the continued development of ISIS-SOD1$_{Rx}$.

Intellectual Property Sale and Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

We have an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology, including as it relates to our second generation antisense drugs and to double-stranded siRNA therapeutics. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to our suite of RNase H patents.

Integrated DNA Technologies, Inc.

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

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

Abbott Molecular Inc.

In January 2008, we and our former subsidiary, Ibis Biosciences, entered into a Strategic Alliance Master Agreement and a Call Option Agreement with AMI pursuant to which:

- In 2008, AMI invested $40 million in Ibis providing the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics; and

- We granted AMI an exclusive call option to acquire from us all remaining Ibis capital stock.

In December 2008, AMI exercised the call option and we, Ibis and AMI executed a stock purchase agreement. Under the stock purchase agreement, AMI purchased the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009. AMI's initial investments, along with the $175 million AMI paid at closing, resulted in a total acquisition price of $215 million plus the earn out payments described below.

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

We valued each element of the initial transaction and as a result allocated $14.6 million to the initial $20 million stock purchase with the remaining $5.4 million allocated to the call option and the subscription right (the "derivative instruments"). On June 27, 2008, AMI exercised its subscription right and purchased an additional $20 million of Ibis' common stock. In December 2008, AMI exercised its call option to purchase the remaining equity ownership in Ibis from us for a closing purchase price of $175 million. As a result, we have reclassified the consolidated financial statements for all periods presented to reflect Ibis as discontinued operations because Ibis meets the criteria for a component of an entity under SFAS 144. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, now a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid us a $2 million upfront fee and agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. During 2004, we earned $4 million in milestone payments, and our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. During 2008, 2007 and 2006, because of our agreement with Drug Royalty Trust 3, or DRT, as described below we did not recognize any revenue from our relationship with Eyetech.

Drug Royalty Trust 3, successor in interest to Drug Royalty USA, Inc.

In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA, Inc., who subsequently transferred its interest to DRT. To date, we have received a total of $23 million under this arrangement. We and DRT are sharing the royalty rights on Macugen from Eyetech through 2009. After 2009, we retain all royalties for Macugen. Through 2009, DRT will receive the royalties on the first $500 million of annual sales of Macugen. We and DRT will each receive 50% of royalties on annual sales between $500 million and $1 billion. We retain 90% of all royalties on annual sales in excess of $1 billion and 100% of all royalties after 2009. We have retained all milestones payable to us by Eyetech under the license agreement. During 2008, we did not recognize any revenue under this arrangement, compared to $7 million and $8 million for 2007 and 2006, respectively. As collateral for our obligations under the sale agreement, we granted DRT a first priority security interest in the patents licensed by us to Eyetech under the license agreement and in the license agreement itself.

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. Our Consolidated Balance Sheets at December 31, 2008 and 2007 included deferred revenue of $200,000 related to our agreements with Roche Molecular Systems. During 2008, 2007 and 2006, we recognized revenue of $1.2 million, $807,000 and $200,000, respectively, from our relationship with Roche Molecular Systems.

Regulus Collaborations

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

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

GlaxoSmithKline

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

Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock. Regulus is also eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In addition to the potential of up to nearly $600 million Regulus could receive in license and milestone payments, Regulus would also receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

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

8. Segment Information and Concentration of Business Risk

Segment Information

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

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

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

The following is segment information for the years ended December 31, 2008, 2007 and 2006 (in thousands).

Year ended December 31, 2008	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 96,743	$ 2,110	$ 98,853
Licensing and royalty	8,337	—	8,337
Total segment revenue	$ 105,080	$ 2,110	$ 107,190
Loss from operations	$ (5,139)	$ (7,921)	$ (13,060)
Total assets as of December 31, 2008 (1)	$ 535,011	$ 23,677	$ 558,688

Year ended December 31, 2007	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 22,200	$ 119	$ 22,319
Licensing and royalty	36,025	—	36,025
Total segment revenue	$ 58,225	$ 119	$ 58,344
Loss from operations	$ (32,014)	$ (905)	$ (32,919)
Total assets as of December 31, 2007 (1)	$ 242,038	$ 10,446	$ 252,484

Year ended December 31, 2006	Drug Discovery and Development	Corporate	Total
Revenue:			
Research and development	$ 5,418	$ —	$ 5,418
Licensing and royalty	9,441	—	9,441
Total segment revenue	$ 14,859	$ —	$ 14,859
Income (loss) from operations	$ (65,754)	$ 536	$ (65,218)

(1) Total assets do not include $15.5 million and $6.4 million of assets held for sale as of December 31, 2008 and 2007, respectively.

Concentrations of Business Risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10% or more of our total revenue, was as follows:

	2008	2007	2006
Partner A	45%	0%	0%
Partner B	30%	23%	0%
Partner C	11%	9%	0%
Partner D	4%	45%	5%
Partner E	0%	12%	54%

Contract receivables from three significant partners comprised approximately 25%, 18% and 14% of contract receivables at December 31, 2008. Contract receivables from four significant partners comprised approximately 32%, 17%, 14% and 12% of contract receivables at December 31, 2007.

9. Restructuring Activities

For the year ended December 31, 2006, we recorded a benefit of $536,000 associated with our restructuring activities resulting from our strategic decision to focus our resources on key programs. In 2006, we successfully negotiated a contract modification settlement with one of our vendors. The amount of the contract termination cost was $265,000 less than the amount that we had previously accrued. Additionally, we negotiated a lease termination agreement with the landlord of a building that we vacated in 2005 as part of the restructuring activities. The early termination of the lease resulted in a benefit of approximately $350,000 over what we had previously accrued. We included these benefits in the restructuring activities for the year ended December 31, 2006.

10. Employee Post Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($15,500 and $20,500 in 2008 for employees under 50 years old and over 50 years old, respectively). We made approximately $467,000, $414,000 and $362,000 in matching contributions for the years ended December 31, 2008, 2007 and 2006, respectively.

11. Legal Proceedings

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under our agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery is in its early stage. We will continue to represent and defend Ibis Biosciences in this matter.

12. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2008, and 2007 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2008 Quarters				
Revenue(1)	$ 18,375	$ 29,703	$ 29,463	$ 29,649
Operating expenses(1)	24,616	28,622	29,287	37,725
Income (loss) from operations(1)	(6,241)	1,081	176	(8,076)
Net income (loss) applicable to common stock	$ (4,285)	$ (2,208)	$ 3,188	$ (8,658)
Basic and diluted net income (loss) per share(2)	$ (0.05)	$ (0.02)	$ 0.03	$ (0.09)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2007 Quarters				
Revenue(1)	$ 874	$ 1,922	$ 33,993	$ 21,555
Operating expenses(1)	19,831	19,802	23,820	27,810
Income (loss) from operations(1)	(18,957)	(17,880)	10,173	(6,255)
Net loss applicable to common stock(3)	$ (13,020)	$ (11,024)	$ (105,304)	$ (6,957)
Basic and diluted net loss per share(2)(3)	$ (0.16)	$ (0.13)	$ (1.25)	$ (0.08)

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

(2) 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.

(3) Includes $125.3 million excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis incurred during the third quarter of 2007.

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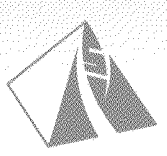

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