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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, 2007

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 o

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

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 o

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

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

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

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

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 $682,790,232 as of June 30, 2007.*

The number of shares of voting common stock outstanding as of March 6, 2008 was 92,943,312.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement for the fiscal year ended December 31, 2007 to be filed on or about April 18, 2008 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 4, 2008 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 87 to 92 incorporates several documents by reference as indicated therein.

* Excludes 12,057,915 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, 2007. 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., our Ibis Biosciences subsidiary and our Regulus Therapeutics joint venture. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, 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.

TRADEMARKS

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

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

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics LLC.

Vitravene® is a registered trademark of Novartis AG.

Orasense™ is a trademark of Isis Pharmaceuticals, Inc.

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 to create a broad pipeline of first-in-class drugs. Through our highly efficient and prolific drug discovery platform, we can expand our drug pipeline and our partners' drug 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 conduct early development on these drugs to key value inflection points. Because we can discover more drugs than we can develop, our plan is to discover new drugs, outlicense our drugs to partners and build a growing annuity of milestone payments and royalty income. In this way, we maximize the value of the drugs we discover by licensing our drugs to partners at key development points, which allows us to focus on utilizing our antisense technology platform to discover new drugs. At the same time, we benefit from our partners' expertise to develop, commercialize and market our drugs. For example, we partner our drugs with leading pharmaceutical companies, such as Bristol-Myers Squibb Company, Genzyme Corporation, Eli Lilly and Company and Ortho-McNeil, Inc. as well as with smaller satellite companies that have expertise in specific disease areas. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam Pharmaceuticals, Inc., Ercole Biotech, Inc. and most recently, Regulus Therapeutics LLC, our joint venture focused on microRNA therapeutics. We explore the technology beyond antisense with additional opportunities in infectious disease identification through our Ibis Biosciences, Inc. subsidiary and in the discovery and development of aminoglycoside and aptamer drugs though our technology partners, Achaogen, Inc. and Archemix, respectively. All of these aspects fit into our unique business model and create continued shareholder value.

Through the efficiency of our powerful technology platform we can discover more drugs and drug candidates than we can afford to develop ourselves. As a result, our drug pipeline continues to mature as our drugs advance in clinical development and we introduce new drugs into the development pipeline. Our partnership strategy has allowed us to maintain an internal focus on our key therapeutic franchises in the areas of cardiovascular and metabolic diseases while also enabling us to create an expansive pipeline with multiple partnerships in cancer, neurodegenerative, inflammation, ocular, and other disease areas.

The success of our business can be measured in part by our notable pharmaceutical partnerships for our key cardiovascular and diabetes drugs, which we completed in 2007 and early 2008, and include BMS, OMI and, most recently, Genzyme. These three partnerships in combination with additional partnership activity in 2007 and early 2008 generated an aggregate of nearly $450 million in upfront cash payments and the potential to earn over $1.9 billion in milestone payments of which approximately $270 million has been received to date. We also will share in the future commercial success of the drugs resulting from these partnerships through profit sharing or royalties. Our positive growth within the last year is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

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 second generation antisense drugs can work in man. With mipomersen we have additional evidence, as we have shown with other second generation 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 the successes related to our drug pipeline, we have taken the first steps to evolve our Ibis subsidiary toward larger commercial markets, such as clinical diagnostics, through Ibis' partnership with Abbott Molecular Inc. Ibis is a product of our innovative technology, and, in 2007, we began commercializing the Ibis T5000 Biosensor System, a revolutionary biosensor system that can simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. Together with Abbott, Ibis intends to expand the commercial opportunities for the Ibis T5000 Biosensor System into the larger clinical diagnostic market. Abbott's initial $20 million equity investment in Ibis and Abbott's expertise in clinical diagnostics will provide Ibis the necessary capital and focus to move quickly toward that goal. Abbott also has the option to acquire the remaining equity of Ibis for a total purchase price of $215 to $230 million, a reflection of the valuation that Abbott places on Ibis and the value we have built through our Ibis business. If Abbott exercises its option, we will continue to benefit through earn out payments based on future commercial sales.

We protect our proprietary RNA-based technologies and products through our substantial and vast patent estate of more than 1,500 issued patents. We remain one of the largest patent holders in the U.S., and with our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology, our drugs, and the Ibis T5000 Biosensor System—they also form the basis for lucrative licensing and partnering arrangements.

Below is a list of some of our key accomplishments for 2007 and early 2008.

2007 and Early 2008 Business Highlights

Drug Development Highlights

Our cardiovascular franchise matured appreciably during the last year, with mipomersen at the forefront. The clinical success of mipomersen has added significant value to our entire drug development pipeline.

- Mipomersen (formerly ISIS 301012) continues to demonstrate an excellent safety and efficacy profile supported by strong Phase 2 clinical results in all patient populations tested. As a result, we initiated registration studies of mipomersen in familial hypercholesterolemia patients.

- We established a strategic alliance with BMS for the discovery and development of antisense drugs targeting PCSK9, an important regulator of the LDL-receptor.

- We initiated IND-enabling studies of ISIS 353512, our antisense drug that targets C-reactive protein, in partnership with the Korea Institute of Technology.

Our metabolic disease franchise continued to expand with the addition of new diabetes drugs into development, and new research efforts toward attractive targets for the treatment of obesity.

- We continued our Phase 2 studies of ISIS 113715 for the treatment of type 2 diabetes in patients on stable sulfonylurea treatment. In humans and preclinical studies, ISIS 113715 demonstrated reductions in blood glucose without causing low blood sugar, called hypoglycemia, weight gain or nausea.

- We initiated Phase 1 studies of ISIS 325568, our antisense drug partnered with OMI that targets the glucagon receptor, GCGR.

- We identified a development candidate, ISIS 377131, an antisense drug also partnered with OMI that targets the glucocorticoid receptor, GCCR.

- We added ISIS 388626 to our development pipeline. ISIS 388626 targets SGLT2, a protein that is responsible for glucose re-absorption in the kidney.

Cancer continues to be a disease in which antisense drugs could make a profound difference in treatment options. Our partners are developing antisense drugs discovered by us to treat cancer.

- OncoGenex Technologies Inc. reported encouraging Phase 2 data for OGX-011, an antisense drug that targets clusterin, in several studies in patients with advanced prostate or lung cancers. The most recent study showed that OGX-011 was well tolerated in combination with certain chemotherapy agents and showed ongoing survival durations that were more favorable than with the chemotherapy agents alone.

- OncoGenex initiated Phase 1 clinical studies of OGX-427, an antisense drug that targets HSP27, a cell survival protein that is overly abundant in cancer cells.

- Lilly advanced its Phase 1 studies of LY2275796, which targets eIF-4E, a protein involved in tumor progression, and in the *Journal of Clinical Investigation*, we and Lilly published preclinical study results that support the therapeutic potential of LY2275796.

We are exploring new applications and disease indications for antisense drugs to treat neurodegenerative diseases and other diseases for which antisense drugs are uniquely suited.

- We were granted orphan drug status for ISIS 333611, an antisense drug in IND-enabling studies that targets SOD1 for the treatment of an inherited, aggressive form of ALS, which is also known as Lou Gehrig's disease. IND-enabling preclinical studies are being funded by the ALS Association and the Muscular Dystrophy Association.

- We initiated a program to discover and develop antisense drugs to treat Huntington's Disease in collaboration with CHDI, Inc., which is providing us with nearly $10 million in funding for the program.

- Antisense Therapeutics Limited recently licensed ATL1102 to Teva Pharmaceutical Ltd. ATL1102 is an antisense drug discovered by us and licensed to ATL, and is currently in Phase 2 studies for the treatment of multiple sclerosis.

- iCo Therapeutics Inc. initiated Phase 1 studies of iCo-007, an antisense drug discovered by us for the treatment of various eye diseases. We received a $1.25 million milestone payment in equity for the initiation of this study.

Partnership Highlights

We added three major new pharmaceutical partners for drugs in our cardiovascular and metabolic franchises, underscoring the confidence of the industry in the promise of antisense drugs for treatment of chronic conditions such as these.

- We licensed mipomersen to Genzyme as part of a strategic alliance that includes a $150 million equity investment, an upfront licensing fee of $175 million, over $1.5 billion in milestone payments, and a share of profits on mipomersen and follow-on drug(s) ranging from 30 to 50% of all commercial sales. As part of the alliance, Genzyme became a preferred development partner for us for drug programs in CNS and certain rare diseases.

- We licensed two type 2 diabetes drugs that target GCGR and GCCR to Johnson & Johnson's OMI for a $45 million upfront licensing fee and could receive more than $230 million in milestone payments for antisense drugs targeting GCGR and GCCR, and we established a research collaboration with OMI to identify additional antisense drugs to treat metabolic diseases. We received the first development milestone payment of $5 million under this collaboration.

- We licensed our lipid-lowering PCSK9 program to BMS for a $15 million upfront licensing fee and up to $168 million in milestone payments.

We expanded clinical opportunities for our drugs by licensing several antisense drugs that are outside of our key therapeutic focus areas to companies with disease-area expertise devoted to optimizing the future development of these drugs.

- We licensed ISIS 369645, an inhaled antisense drug, to Altair Therapeutics Inc. for the treatment of respiratory diseases.

- We entered into a collaboration with Excaliard Pharmaceuticals, Inc. to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring.

- We licensed alicaforsen, an antisense drug targeting ICAM 1 for ulcerative colitis, to Atlantic Healthcare (UK) Limited.

We demonstrated the value of our technology innovation and dominant intellectual property through partnerships with industry leaders in a variety of related areas.

- We received $26.5 million under our collaboration with Alnylam, associated with Alnylam's transaction with F. Hoffmann-La Roche Ltd.

- We licensed technology to Archemix for aptamer drug applications in exchange for milestones and royalties on aptamer drugs developed by Archemix that incorporate our proprietary chemistries or manufacturing methods; we received the first milestone payment from Archemix for the advancement of Archemix' aptamer drug into Phase 2a studies.

Corporate Highlights

We improved our financial position significantly in 2007, strengthening our balance sheet and reducing our net operating loss.

- We refinanced our convertible debt which extended the maturity of the debt, strengthened our balance sheet, and reduced our cash interest payments by approximately $2.6 million annually due to the lower coupon rate.

- We purchased Symphony GenIsis, Inc. relatively early in the term of that financing arrangement saving us approximately $75 million in the predetermined purchase price, regaining full ownership of mipomersen, which we licensed to Genzyme, and the GCGR and GCCR drugs, which we licensed to OMI.

- As a result of our partnering strategy we were able to reduce our pro forma net operating loss guidance by $40 million over the course of 2007.

We strengthened our leadership team with the addition of

- Jeffrey M. Jonas, M.D. to lead Clinical Development, Preclinical Development, Regulatory Affairs, and Quality Assurance and Compliance. Dr. Jonas was formerly Chief Medical Officer and Executive Vice President at Forest Laboratories, Inc.

Regulus Highlights

We and Alnylam founded Regulus and hired senior management to lead the joint venture company in discovering and developing antisense drugs targeting microRNAs.

- Kleanthis G. Xanthopoulos, Ph.D. was appointed President and Chief Executive Officer of Regulus. Dr. Xanthopoulos is the co-founder and former President and Chief Executive Officer of Anadys Pharmaceuticals, Inc.

- Peter S. Linsley, Ph.D. was appointed Chief Scientific Officer of Regulus. Dr. Linsley was Executive Director of Cancer Biology at Merck Research Laboratories, and was previously Vice President of Research of Rosetta Inpharmatics.

Ibis Highlights

Our Ibis subsidiary gained a strategic partner, Abbott, which will enable Ibis to aggressively prepare to enter larger commercial markets, including hospital-acquired infection control and clinical diagnostics. Ibis also successfully completed its first full year of commercializing the Ibis T5000 Biosensor System.

- Abbott invested $20 million in Ibis and now owns 10.25% equity in Ibis at a post money valuation of $215 million, with the option to invest an additional $20 million in Ibis for a total equity holding of 18.6%.

    - Abbott acquired the option to purchase the remaining shares of Ibis for a total purchase price of $215 to $230 million.

    - If Abbott exercises its option to acquire Ibis, we will receive an earn out tied to the achievement of specific cumulative sales.

- Ibis placed eight instruments, including placements with research hospitals.

- Ibis finished constructing its commercial assay kit manufacturing facility.

- Ibis received over $12 million in contracts and grants during 2007 to advance the detection and identification of infectious organisms for a broad range of applications, including biodefense.

Drug Discovery and Development

Introduction to Drug Discovery

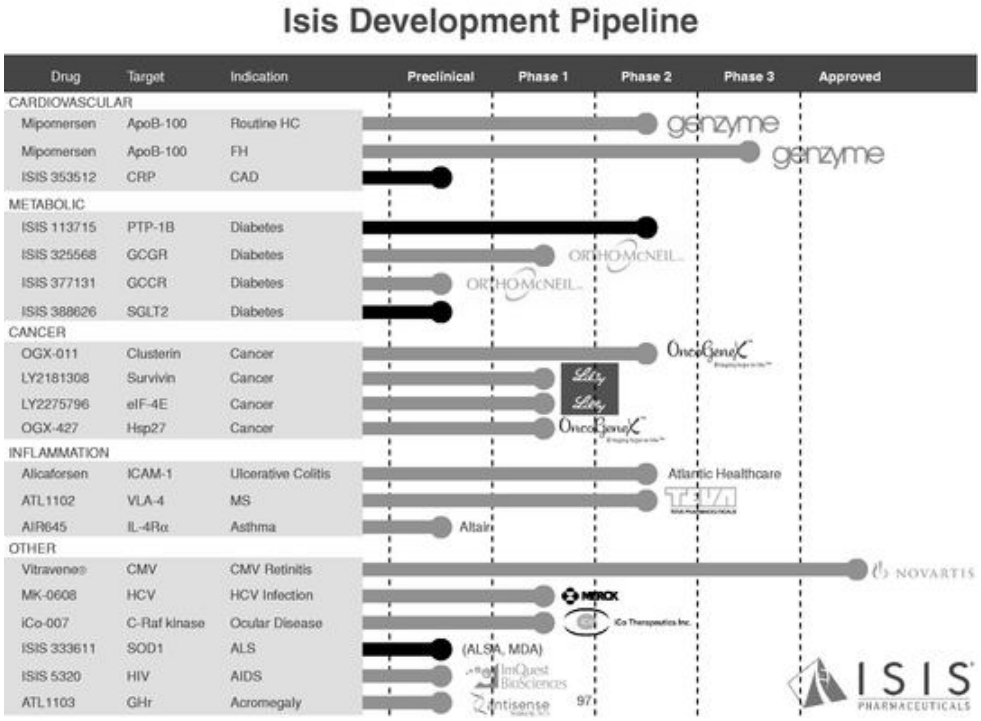
Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production or improper protein activity. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense drugs are different from traditional small molecule drugs because they interrupt the production of disease-causing proteins by targeting RNAs, or ribonucleic acids. 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 Drugs In Development

We are the leader in the discovery and development of an exciting new class of drugs called antisense drugs. Our proprietary technology 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.

With our expertise in discovering and characterizing novel antisense inhibitors, our scientists can modify the properties of our antisense drugs for optimized use with particular targets. Over the past decade, 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 develop new formulations that expand the therapeutic and commercial opportunities of our pipeline. We and our partners are studying them in a variety of formulations for both systemic and local delivery. These advancements along with the shared manufacturing and analytical processes, shorten our timeline from initial concept to the first human dose. The following table lists our approved product and each of our and our partners' drugs in development, their targets, disease indications and the development status of each. We also have a significant research program that we expect will 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.



Cardiovascular Franchise

Cardiovascular disease is the leading cause of death in the United States. Its underlying cause 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 the prevention and management of cardiovascular disease. Another independent risk factor for cardiovascular disease is high levels of C-reactive protein, or CRP, which is associated with significantly worse outcomes in patients with cardiovascular disease.

Mipomersen (ISIS 301012)—In October 2007, the United States Adopted Names Council, USAN, approved the generic name for ISIS 301012, mipomersen sodium. Mipomersen is now the nonproprietary name we use in all of our communications regarding ISIS 301012, our cholesterol-lowering drug. Mipomersen reduces 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. Cholesterol can be carried in the bloodstream in a variety of forms, with high-density lipoprotein, or HDL, being the good form, and low-density lipoproteins or LDL, and very low-density lipoproteins, or VLDL, being the bad or atherogenic forms directly involved in heart disease. ApoB-100 is found in

both bad types of cholesterol particles. ApoB-100 is a target that the pharmaceutical industry has long recognized as an attractive point of intervention but to date it has proven to be undruggable using traditional small molecule approaches.

In early 2008, we licensed mipomersen to Genyzme as part of a strategic transaction that included a profit sharing arrangement, which will enable us to continue to benefit from mipomersen's success. We are developing mipomersen as a new treatment for high cholesterol. We plan to develop mipomersen for patients who are unable to achieve target cholesterol levels with statins alone, as well as for patients who are intolerant of statins. This is a large market opportunity in a chronic disease, where new treatment options are still needed. The current recommendations from the National Cholesterol Education Program's Adult Treatment Panel III are for LDL-cholesterol goals of less than 100 mg/dL for High Risk patients and less than 130 mg/dL for Moderately High Risk patients. Further reductions to these LDL targets have been proposed, and less than 70 mg/dL and 100 mg/dL are the optional targets for the High Risk and Moderately High Risk groups, respectively. Roughly 80% of the 20 million people in the U.S. in the High Risk category (or 16 million people in the U.S.) are not meeting LDL targets on their current lipid-lowering therapies, and 5 million of the more than 10 million Moderately High Risk patients are not achieving target levels taking statins alone. In other words, more than 20 million patients in the U.S. are in need of additional therapies to complement current lipid lowering drugs, including statins.

We are also developing mipomersen for patients with familial hypercholesterolemia, or FH, a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease. The FDA granted mipomersen Orphan Drug designation for treatment of patients with homozygous FH, or HoFH, a very rare, especially severe form of the disease that occurs in about one in a million patients. Orphan Drug designation is a designation that provides a path for clinical studies in severe populations with an accelerated registration. Heterozygous FH, or HeFH, is far more common, occurring in approximately one in 500 patients. We estimate that there are over a half million patients in the U.S. with HeFH, which we feel represents an attractive market opportunity of high risk patients.

From our experience in FH patients, mipomersen continues to be an extremely active lipid lowering drug, lowering multiple independent risk factors for cardiovascular disease, including apoB, LDL-C, triglycerides and Lp(a). In 2007 we presented results of Phase 2 studies in FH patients demonstrating that at a dose of 300 mg/week, mipomersen lowered LDL-C by approximately 50% and significantly reduced all other atherogenic lipids, as well as Lp(a), in these severely affected patients who were concurrently being treated with maximally tolerated lipid lowering therapies including high-dose statins and ezetimibe. Our evaluation of these patients is continuing in our open-label extension study. In October 2007, we reported interim safety results of this extended exposure study showing that mipomersen continued to be well tolerated even after weekly doses for six months or longer. Since then, we have initiated pivotal studies that are intended to support filing with the FDA for approval of mipomersen in patients with familial hypercholesterolemia.

In parallel with our mipomersen program in FH patients, we are conducting Phase 2 trials to address the larger commercial market represented by High Risk patients with high cholesterol who are not reaching their target cholesterol levels despite maximally tolerated lipid-lowering therapies. Throughout 2007, we reported positive results from Phase 2 studies in patients with high cholesterol who received mipomersen as monotherapy or as an add-on to stable doses of statins. We have shown mipomersen to be equally active as a single agent and in combination with moderate and maximally tolerated lipid lowering therapy, that when dosed for three months at 200 mg/week mipomersen lowered LDL-C levels nearly 50% beyond the levels achieved with statins alone. In November 2007, we presented an integrated Phase 1 & 2 safety analysis that included data from more than 250 subjects who had been treated with mipomersen. The integrated safety analysis continues to demonstrate that the effects of mipomersen are consistent and predictable from patient to patient and group to group and equally active in all patient populations studied, both with long term treatment and retreatment.

We advanced clinical development of mipomersen in multiple high risk patient populations, which we believe significantly increased the value of mipomersen, and enabled us to license mipomersen on very favorable terms to Genzyme. In conjunction with Genzyme, we anticipate the completion of the pivotal study in HoFH patients and a New Drug Application, or NDA, filing in 2009. We continue to pursue our mipomersen development plan with treatment in other high risk patient populations and anticipate additional safety results this year. In 2007 we demonstrated in preclinical studies that in addition to reducing LDL-C, antisense inhibition of apoB also promoted changes in lipid metabolism in the liver, thereby preventing accumulation of fatty acids that might otherwise be expected due to lack of production of LDL-C. This was an important finding because it provided more support for the safety profiles we have observed in patients receiving mipomersen. We look forward to potential additional indications and opportunities, along with continued potent activity and an attractive safety profile that may result from trials concluding over the next year.

ISIS 353512—ISIS 353512 is a generation 2.2 antisense drug that targets C-reactive protein, or CRP. Excessive amounts of CRP have been linked to coronary artery disease and 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 preclinical studies, ISIS 353512 produced dramatic suppression of liver and serum CRP levels in monkeys. In additional animal studies, ISIS 353512 dramatically reduced human CRP levels in transgenic mice. Based on these results, we initiated development activities for ISIS 353512. The Korea Institute of Technology is conducting toxicology and other IND-enabling studies for ISIS 353512 through our agreement that enables us to advance ISIS 353512 development and reduce preclinical costs substantially in exchange for a nominal royalty. We anticipate initiating a Phase 1 safety study of ISIS 353512 in 2008.

Cardiovascular research—We are continuing to build our cardiovascular disease franchise by evaluating additional potential drug targets that influence the onset and progression of cardiovascular disease. We intend to expand our cardiovascular franchise with additional drugs to treat various aspects of cardiovascular disease through complimentary mechanisms. In addition, we continue to add to our scientific understanding of our drugs and disease targets, including the biological processes that are linked to our disease targets and the impact of our drugs on these processes. For instance, PCSK9 is a promising target for lowering cholesterol. It has been shown that humans with genetic mutations leading to increased levels of PCSK9 have severe high cholesterol. We established a strategic alliance with BMS for the discovery and development of antisense drugs targeting PCSK9 for the treatment of cardiovascular disease. In 2008, we and BMS expect to advance into development a drug targeting PCSK9 for the treatment of cardiovascular disease. Additional research may enable us to continue to identify other novel disease intervention targets that can lead to the development of potent and highly effective drugs to treat cardiovascular disease.

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%-95% of those cases.

ISIS 113715—ISIS 113715 is our second generation 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.

PTP-1b has long been recognized 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 effecting 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 results of this Phase 2 study during 2008.

ISIS 325568—ISIS 325568 is a generation 2.2 antisense drug that targets glucagon receptor, or GCGR. Our GCGR program was licensed to OMI 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, ISIS 325568 led to improved glucose control and reduced levels of blood triglycerides without producing hypoglycemia. While this is justification enough to pursue GCGR as a therapeutic target, the additional activity of ISIS 325568 in increasing circulating glucagon-like peptide, or GLP-1, makes it an even more attractive drug for development. GLP-1 is a hormone that helps to preserve pancreatic function, enhancing insulin secretion.

ISIS 325568 is currently being evaluated in a Phase 1 study designed to assess activity, including its effect on liver glucose production, as well as safety and the characteristics of ISIS 325568 that determine its effectiveness as a drug. The initiation of this trial marked the completion of our first milestone with OMI in our metabolic disease collaboration, and we believe that, in addition to safety, this trial will provide the opportunity to demonstrate proof-of-concept in humans. Working with OMI, we expect to complete this Isis initiated phase 1 safety study of ISIS 325568 within the next year, and we expect OMI will initiate a phase 2 study on ISIS 325568.

ISIS 377131—ISIS 377131 is a second generation 2.2 antisense drug that targets the glucocorticoid receptor, or GCCR. Glucocorticoid hormones have a variety of effects throughout the body, including promoting liver glucose production and fat storage. Although inhibition of GCCR has long been recognized as an attractive strategy for development of therapeutics for Type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged development 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—inhibition of GCCR expression in these two organs can lead to systemic side effects. In preclinical studies, Isis has shown that ISIS 377131 has a broad therapeutic profile that includes reduction of blood glucose levels, a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and a reduction in body fat.

ISIS 388626—ISIS 388626 is our latest metabolic disease drug to enter our development pipeline for the treatment of diabetes. ISIS 388626 is a generation 2.2 antisense drug that targets SGLT2 to increase blood sugar excretion thereby reducing blood sugar levels. Because SGLT2 is responsible for

glucose re-absorption in the kidney, blocking that action promotes glucose excretion and lowers blood sugar.

In preclinical studies, inhibition of SGLT2 was very potent in reducing blood glucose levels and glycosylated hemoglobin, or HbA1c, which is a measure of long-term glucose control, without causing low blood sugar, called hypoglycemia. Therefore, we believe that ISIS 388626 could be a potent, highly active drug that will provide significant therapeutic benefits. We anticipate initiating IND-enabling studies for ISIS 388626 in 2008.

Metabolic disease research—We now have four drugs in development to treat type 2 diabetes, each of which acts upon targets in the liver, adipose 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 OMI collaboration, we are working with OMI to identify additional antisense drugs to treat metabolic diseases. Additionally, we are turning more of our research focus to obesity. In 2007 at the American Diabetes Association annual conference we presented data on several exciting obesity targets. 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 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, which we are co-developing and commercializing with OncoGenex. We and OncoGenex designed OGX-011 to inhibit the secreted protein clusterin, which acts as a cell-survival protein and is over-expressed in response to anti-cancer agents, like chemotherapy, hormone ablation and radiation therapy.

In 2007, OncoGenex announced preliminary data from several Phase 2 studies evaluating OGX-011 in combination with chemotherapy in patients with prostate cancer and non-small cell lung cancer, NSCLC. In one prostate cancer study, hormone refractory advanced prostate cancer patients were given once weekly intravenous administration of OGX-011 in combination with chemotherapy. In this study, patients receiving OGX-011 showed prolonged durations of progression-free survival and increased disease stabilization compared with historical controls. Based on the results from this study, OncoGenex is planning a pivotal Phase 3 study to evaluate OGX-011 in combination with chemotherapy. In the ongoing NSCLC study, a majority of the patients experienced either objective tumor responses or disease stabilization. Also in 2007, OncoGenex reported preliminary results of a Phase 2 breast cancer study in which clinical activity was seen for the combination of OGX-011 and docetaxel in patients with metastatic disease, but the results did not meet the pre-determined criteria to expand the trial into a second stage of accrual. Most recently, OncoGenex reported that, in a Phase 2 study for prostate cancer, OGX-011 was well tolerated in combination with certain chemotherapy agents and showed ongoing survival durations that were more favorable than with the chemotherapy agents alone based on historical controls. OncoGenex expects to report additional Phase 2 results for OGX-011 in patients with cancer. Additionally, OncoGenex intends to further evaluate OGX-011 in prostate cancer with the initiation of a Phase 3 study in 2008.

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. Increased Hsp27 production is linked 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 drug, paclitaxel. OncoGenex is currently conducting a Phase 1 clinical study of OGX-427 in patients with breast, ovarian, bladder, prostate or lung cancer. OncoGenex expects to initiate Phase 2 clinical studies of OGX-427 in 2008.

LY2181308—We licensed our anti-cancer drug, LY2181308, to Lilly in 2002, as part of the companies' antisense drug discovery research collaboration in cancer initiated in 2002. This drug targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin 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 studies of LY2181308, and during 2008, expects to initiate a Phase 2 program examining LY2181308's effectiveness against multiple types of cancer.

LY2275796—LY2275796 is the second antisense anti-cancer drug we have licensed to Lilly and is currently in Phase 1 studies. 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 2007 and 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 and Other Drug Development Highlights

In addition to our cardiovascular and metabolic disease and cancer franchises, we are committed to expanding our antisense technology into disease areas that are currently underserved with current treatment options. We are particularly interested in the opportunities for a number of antisense drugs to treat neurodegenerative diseases, where there is a large unmet need for new treatment options. We have initiated two programs to develop drugs for the treatment of neurodegenerative diseases, and both are funded through grants. Our most advanced of the two programs, ISIS 333611 to treat ALS, is currently in preclinical toxicology studies. In addition to our internal programs, we have been successful in developing novel drugs and licensing them to highly focused companies that have the specific expertise and resources to continue development of these drugs.

AIR645 (ISIS 369645)—We have licensed AIR645, formerly ISIS 369645, to newly formed Altair, a venture capital funded biotechnology company that was created to focus 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, IL-4R-alpha that inhibits IL-4 and 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 have shown that a mouse-optimized antisense inhibitor of IL-4R-alpha potently reduced target messenger RNA, or mRNA, and protein levels, and had 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. Altair plans to initiate Phase 1 evaluation of AIR645 in 2008.

Alicaforsen (ISIS 2302)—Now under license to Atlantic Healthcare, alicaforsen selectively inhibits 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 when their diseased colons are removed. In December 2004, we released the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen was well tolerated and produced significant and long-lasting disease improvement, as measured by changes in Disease Activity Index scores and other indicators of disease. In addition, data from a 2003 clinical trial for an enema formulation of alicaforsen demonstrated an improvement in clinical disease symptoms of up to nine months in patients with pouchitis. In 2007, we licensed alicaforsen to Atlantic Healthcare, initially for pouchitis and eventually for ulcerative colitis and other inflammatory diseases. Atlantic Healthcare plans to initiate a Phase 3 program for pouchitis during 2008.

ATL1102—Now under license to Teva, ATL1102 is a generation 2.2 antisense inhibitor of CD49d, which is a subunit of Very Late Antigen-4, or VLA-4. Studies in animal models have demonstrated that inhibition of VLA-4 has a positive effect on a number of inflammatory diseases, including multiple sclerosis. In December 2001, we licensed ATL1102 to ATL. Based on the results of a dose-escalating Phase 1 study of ATL1102 that showed that 6 mg/kg/week of ATL1102 appeared well tolerated, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis for which results are expected to be reported this year. In 2008, ATL licensed ATL1102 to Teva, which has responsibility for continued development of ATL1102 beyond ATL's current Phase 2 study.

ATL1103—ATL1103 is a second generation antisense drug targeting growth hormone receptor, or GHr. Consequently, it reduces the levels of circulating insulin-like growth factor-1, or IGF-1, produced in the liver, which is a hormone that contributes to various diseases including the growth disorder 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 animal studies, ATL1103 demonstrated significant reductions in IGF-1 levels in the blood. ATL is planning to initiate IND-enabling studies of ATL1103 in 2008.

iCo-007—We licensed iCo-007 to iCo for the treatment of various eye diseases that occur as complications of diabetes, including diabetic macular edema and diabetic retinopathy. 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 c-Raf kinase inhibition could be valuable in the treatment of 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 between 50% and 80% of type 2 diabetics develop retinopathy. iCo has advanced iCo-007 into Phase 1 studies for which we earned a milestone payment.

ISIS 333611—ISIS 333611 is our first drug to enter development for the treatment of an inherited, aggressive form of ALS, which is also known as Lou Gehrig's disease. ISIS 333611 was granted Orphan Drug designation by the FDA for the treatment of ALS. The drug is administered directly into the central nervous system by a small pump that infuses drug into the cerebral spinal fluid. This type of administration is called intrathecal infusion.

In animal models, researchers have demonstrated that ISIS 333611, when delivered into the cerebral spinal fluid, inhibits Cu/Zn superoxide dismutase, or SOD1, a molecule that is associated with an inherited, aggressive form of ALS. In July 2006, researchers reported in the Journal of Clinical Investigation that treatment with ISIS 333611 prolongs life in rats that show many features of ALS. By delivering ISIS 333611 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 IND-enabling studies of ISIS 333611.

ISIS 5320—ISIS 5320, a phosphorothioate oligonucleotide aptamer drug, specifically and potently inhibits the attachment of HIV to target cells by physically interfering with the interaction of the HIV receptor glycoprotein 120, or gp120, with CD4 on target cells. In 2006, we licensed ISIS 5320 to ImQuest Pharmaceuticals, Inc. The safety of ISIS 5320 has been demonstrated in human clinical trials as a treatment for systemic HIV infection and ImQuest is now pursuing it as a topical microbicide.

MK-0608—This drug, which inhibits hepatitis C virus replication, resulted from a drug discovery collaboration between Merck & Co., Inc. and us. Merck initiated Phase 1 development in November 2006 for which we earned a milestone payment.

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

Antisense Technology

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

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

When a cell transcribes information from a DNA gene into mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template and information stored in the DNA strand is copied into a complementary mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in so doing, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the synthesis of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the "sense" strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Specifically, 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 the basic 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 Technologies

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 and Ercole.

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

Modulation of alternative splicing seeks to control the process by which a single gene can lead to several 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. This process is called splicing. Using antisense technology, we have been able to control how these stretches of RNA are spliced back together. This provides another way to control the production of a disease-causing protein. Through our relationship with Ercole, we are combining both companies' alternative splicing expertise to discover antisense drugs that regulate RNA splicing.

Other Oligonucleotide Opportunities

Oligonucleotide molecules can also be designed 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.

MicroRNAs

There are many different types of RNA that exist within the body, and our antisense technology is not limited to targeting protein coding mRNA sequences, but rather we can apply the principals of our oligonucelotide chemistry to develop other RNA-targeted drugs. One emerging area is microRNAs. MicroRNAs are small RNA molecules that work as natural antisense oligonucleotides and appear to have critical functions in controlling the process of gene expression. These molecules may serve as drug targets or as drugs themselves. To date, there are more than 500 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of approximately one-third of all human genes. In September 2007, we announced the formation of Regulus, a joint venture we formed with Alnylam. Regulus will focus on the discovery, development, and commercialization of microRNA therapeutics.

Regulus Therapeutics LLC

In September 2007, we and Alnylam established Regulus as a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Because microRNAs regulate whole networks of genes that can be involved in discrete disease processes, microRNA therapeutics represent a new approach to target the pathways of human disease. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA therapeutics. In addition, Regulus has assembled a strong leadership team, as well as the foremost authorities in the field of microRNA research to lead this new venture.

Regulus Business

We and Alnylam both granted Regulus exclusive licenses to our intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Tuschl IV" and "Esau" patents. Alnylam made an initial investment

of $10 million to balance venture ownership. Thereafter, we and Alnylam will share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. Regulus is operated 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 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 Technology

Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs regulate the expression of broad networks of genes and biological pathways, microRNA therapeutics define a new and potentially high-impact strategy to target multiple points on disease pathways.

Conventional mRNAs are the genetic instructions for creating proteins through the process of translation. Recently, an entirely new category of RNAs was discovered: microRNAs. Like other RNAs, microRNAs are also genetically encoded. However, these small microRNAs do not serve as instructions for creating proteins but instead regulate the expression of other genes. To date, scientists have identified more than 500 microRNAs in the human genome that the scientists believe regulate the expression of approximately one-third of all human genes. Thus, microRNAs may act as master regulators for physiological pathways or genetic networks to achieve integrated biological functions. This ability to affect the expression of multiple genes in the pathway of disease makes microRNAs an exciting new platform for drug discovery and development, and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

Therapeutic programs

To date, microRNAs have been implicated in several disease areas, such as cancer, viral infection, and metabolic disorders. Regulus is currently focusing on several of these disease areas, including microRNA therapeutics that target miR-122, an endogenous liver-specific host gene also required for viral infection by hepatitis C virus, or HCV, lipid metabolism and steatosis. Regulus is actively exploring additional areas for development of microRNA therapeutics, including cancer, other viral diseases, metabolic disorders, and cardiovascular diseases.

Ibis Biosciences, Inc.

Ibis is our majority-owned subsidiary that has the potential to revolutionize the way that infectious disease pathogens are identified. Ibis developed and is now commercializing its biosensor technology, including the Ibis T5000 Biosensor System and assay kits. Ibis' T5000 Biosensor System offers a unique solution to rapidly identify and characterize infectious agents. It can identify virtually all bacteria, viruses and fungi and provide information about drug resistance, virulence and strain type of these pathogens within a few hours.

In January 2008, Ibis announced the formation of a strategic alliance with a leader in clinical diagnostics. Abbott invested $20 million in Ibis and acquired 10.25% of Ibis equity. Abbott also received the right to invest an additional $20 million before July 31, 2008 for a total of 18.6 percent of Ibis equity. Abbott's investment in Ibis provides the necessary capital for Ibis to take the next key steps in advancing the technology to larger commercial markets, including clinical diagnostics. Along with the opportunity to participate in Ibis' commercial growth, Abbott received an exclusive option to purchase the remaining equity in Ibis for a total purchase price of $215 million through June 30, 2009, plus an earn out tied to achievement of certain cumulative sales. The total purchase price can increase to up to

$230 million with Ibis' successful completion of pre-negotiated milestones. This strategic alliance couples Ibis with an experienced partner in clinical diagnostics to ensure that Ibis is focused efficiently toward completing the pre-negotiated milestones and commercial success. Since the transaction provides for earn out payments if Abbott ultimately acquires Ibis, our shareholders will continue to benefit from Ibis' success. The earn out payments from Abbott to us 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 calculated based on 5% of cumulative net sales over $150 million through net sales of $2.1 billion and 3% of cumulative 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 not only for the Ibis business, but also for our shareholders.

Ibis Business

The Ibis T5000 Biosensor System enables rapid identification and characterization of bacterial, viral, fungal and other infectious organisms, as well as analysis of human DNA. The Ibis T5000 has the unique ability to rapidly identify a broad range of infectious organisms in a sample without needing to know beforehand which organisms might be present. This powerful new approach to microorganism characterization and detection is fundamentally different than traditional methods requiring prior knowledge of a suspected organism's DNA sequence to enable detection and identification. Historically Ibis' technology research and development has been supported largely by grants and contracts from government agencies, and government funding continues to underwrite development of a number of applications for the Ibis T5000.

The commercialization plan for the Ibis T5000 Biosensor System and related products is a phased commercial progression that takes advantage of near-term opportunities, builds on an existing customer base and moves toward the larger healthcare markets. We have commercialized the Ibis T5000 for various government, epidemiology and clinical research applications, and we are expanding our markets to include hospital-associated infection, or HAI, control. These near-term, non-regulated market opportunities prepare the business and the customers for Ibis' ultimate entry into the clinical diagnostics market. Together with Abbott, we have defined a path to the clinical diagnostics market, and Ibis is currently taking aggressive steps to prepare to address this major commercial opportunity.

Ibis has three commercial business segments: instrument sales, assay kit sales, and assay services conducted on site at Ibis. 2007 was Ibis' first full year of commercialization. In this first commercial year, we have successfully placed a total of eight systems. We continue to reach new customers by expanding our historical government-based business into clinical research and HAI control with placements in hospitals and laboratories of key opinion leaders, such as Johns Hopkins University, Northwestern Memorial Hospital, and University of Texas Medical Branch, Galveston. All of these relationships are laying the groundwork for us to move toward the clinical diagnostics market.

Ibis develops, manufactures and markets Ibis T5000 instruments and assay kits. Ibis is developing, manufacturing and selling Ibis T5000 assay kits and consumables. Currently, we are selling research use only kits for many applications. Examples of these kits include influenza surveillance, *Staphylococcus aureus* genotyping and characterization, antibiotic resistance determination and anthrax genotyping. We continue to develop new kits, and as defined through our agreement with Abbott, we are particularly focused on developing those applications that will be of highest commercial value for the clinical diagnostics market.

Ibis' assay services laboratory represents a key part of the early Ibis business strategy by providing revenue to support initial commercialization activities while instrument installations and kit sales increase. In addition, the assay services laboratory supports the Ibis T5000 sales process by providing customers the opportunity to evaluate the capabilities of the Ibis T5000 Biosensor System prior to making a buying decision.

In addition to its commercial activities, Ibis engages in research and development projects principally supported by government grants and contracts. Historically, government agencies supported development of the Ibis T5000 technology and instrumentation, and currently our government collaborators are funding development of new applications. Also, many of our government partners are also commercial customers of instruments, assay kits and/or assay services.

Ongoing Activities

Our Ibis subsidiary plans to continue commercializing the Ibis T5000 in research markets, including the sale of consumables to existing customers and adding new customers. In our assay services laboratory we plan to continue to analyze customer and collaborator samples through new and existing commercial contracts and grants. We will also continue the development of the Ibis technology and applications with funding from Abbott's investment and our contracts with government agencies. Government agencies have represented a significant source of funding for Ibis. As of December 31, 2007, we had earned $67.8 million in revenue under our government contracts and grants, and we had an additional $8.3 million committed under our existing contracts and grants. We may receive continued funding under these contracts based upon a variety of factors, including whether Ibis accomplishes program objectives or the contracting agency exercises additional contract options. However, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

During 2007 and 2006, revenue generated from agencies of the United States Government totaled 16% and 39%, respectively, of our total revenue. Please refer to Note 7, "Segment Information and Concentration of Business Risk," starting on page F-46 of this report on Form 10-K for additional information about our Ibis subsidiary.

Ibis is committed to advancing the Ibis T5000 Biosensor System into larger commercial markets, including hospital-acquired infection control and clinical diagnostics. Early in 2008, Ibis achieved a key goal to establish a strategic partner in the diagnostics arena and to secure funding to support continued progress in commercial development. Ibis intends to continue expanding its customer base and to place at least eight additional Ibis T5000 Biosensor Systems and will focus on completing the next steps in its Abbott transaction.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a clinical development pipeline of 18 drugs, to create an annuity of milestone payments and royalty revenue and to limit our drug development expenses. In this way, we have remained 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 and metabolic diseases. These are disease areas where 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 the 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, and we license the resulting drugs to pharmaceutical companies and to focused drug discovery and development satellite companies who are dedicated to the advancement of our drugs. Through this strategy we can expand the therapeutic range of antisense drugs into disease areas that are in need of 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 licensing. Each of these categories is discussed in more detail below, along with the relevant partnerships.

Traditional Pharmaceutical Alliances and Licensing

We license 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, we should be able to advance our drugs more rapidly and toward larger markets than we could do on our own. During 2007, we added two pharmaceutical partners, BMS and OMI, both of which licensed early-stage drugs in our core franchises of cardiovascular disease and metabolic disease. These partnerships were important for us in that they demonstrated the industry's confidence in the promise of our technology, and our drugs for the treatment of chronic diseases, in particular. In early 2008, we entered into a licensing agreement for mipomersen with Genzyme with favorable deal terms, including milestones and a profit sharing arrangement that will allow us to continue to benefit from mipomersen's success. Having accomplished these partnerships, we now can develop the majority of our cardiovascular and metabolic disease drugs through early proof-of-concept ourselves prior to licensing, and that is what we expect to do going forward.

Genzyme Corporation

In January 2008, we announced a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. Mipomersen is our lipid-lowering drug targeting apoB-100. As part of the strategic relationship, Genzyme has exclusively licensed mipomersen and will also have preferred access to our future drugs for CNS and certain rare diseases. Genzyme paid us $150 million to purchase five million shares of our common stock for $30 per share and upon the completion of the license agreement Genzyme will also pay us a $175 million upfront license fee for mipomersen. In addition to this initial $325 million, we also have the potential to receive up to $825 million in development and regulatory milestone payments and up to $750 million in commercial milestone payments. Under the agreement, we will also share profits with Genzyme, with our share being 50% for annual revenues of $2 billion or greater, and increasing linearly from 30% to 50% as annual revenues ramp up to $2 billion. We have committed to spend $75 million of development costs over the next few years. Genzyme will take over full development and commercialization responsibilities thereafter.

Genzyme has agreed that it will not sell its Isis stock until the earlier of 4 years from the date of our mipomersen license agreement, the first commercial sale of mipomersen and the termination of the our mipomersen license 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 agreement and 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.

Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with OMI to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMI worldwide development and commercialization rights to two of our diabetes drugs, ISIS 325568 and ISIS 377131, which selectively inhibit the production of GCGR and GCCR, respectively. Additionally, OMI is providing funding to us to support a focused research program in metabolic disease. Under the terms of the agreement, OMI 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 milestones 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 trials of ISIS 325568 for which we earned the first development milestone payment of $5 million. During 2007, we recognized revenue of $13.2 million related to the upfront licensing fee, the milestone payment and the initial research and development funding, which represented 19% of our total revenue for 2007.

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 a period of three years. During 2007, we recognized revenue of $5.2 million related to the upfront licensing fee and the research funding, which represented 8% of our total revenue for 2007. We will also receive up to $168 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestones associated with development of follow-on compounds. BMS will also pay us royalties on sales of products resulting from the collaboration.

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, 2007, we earned milestone payments totaling $1.2 million under the collaboration agreement. Pfizer will also pay us additional milestone payments under the collaboration agreement if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, we will earn milestone payments totaling up to $26.1 million. In addition, under the collaboration agreement, we will receive royalties on the sale of drugs resulting from the collaboration. During 2007, 2006 and 2005, we earned revenue of $445,000, $547,000 and $2.2 million, 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 and a $100 million loan that Lilly provided to us to fund our obligations under the research collaboration. In August 2005, we extended the research collaboration with Lilly to focus on a select number of targets. During the extension, we and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue our efforts to develop and refine antisense technologies. During the extension, we are using collaboration funds to support our scientists and Lilly is supporting Lilly scientists. The extended collaboration provides Lilly access to our patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, we and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries. In connection with the extension, we converted the $100 million loan that Lilly previously provided to us into 2.5 million shares of our common stock.

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, 2007, we have 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 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 royalties on future product sales of these drugs.

During 2007, we earned revenue from our relationship with Lilly totaling $402,000, compared to $1.2 million and $10.8 million in 2006 and 2005, 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 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. During 2007 and 2005, 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

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 a partner who is focused in a particular disease area who shares 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. In 2007, we added Atlantic Healthcare, Altair and Excaliard to our list of drug discovery and development satellite companies.

Antisense Therapeutics Limited

In February 2008, ATL, an Australian company publicly traded on the Australian Stock Exchange that we previously licensed ATL1102 to, licensed ATL1102 to Teva Pharmaceutical Ltd. ATL1102 is currently in Phase 2 studies to assess the safety and activity of the drug in patients with multiple sclerosis. 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.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we extended for an additional two years in January 2007. ATL pays us 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 2007, we recorded revenue of $80,000 related to this collaboration compared to $652,000 and $698,000 for 2006 and 2005, respectively. At December 31, 2007 and 2006, we owned less than 10% of ATL's equity.

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, 2007, we owned less than 10% of Excaliard's equity and we have no significant remaining obligations to perform. In addition, we are eligible to receive development milestone payments and royalties on antisense drugs developed by Excaliard. During 2007, we recognized revenue of $1 million related to a gene target licensing fee.

Altair Therapeutics Inc.

In October 2007, Altair, a venture capital-funded biotechnology company, was created to focus 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 ISIS 369645, an inhaled inhibitor of the IL-4/IL-13 signaling pathways for the treatment of asthma. Altair is solely responsible for the continued development of ISIS 369645. At December 31, 2007, we owned 18 percent of Altair in the form of preferred stock. In addition to the preferred stock, we will receive additional license fees and royalties if ISIS 369645 and other drugs arising out of the research collaboration progress. During 2007, we recognized revenue of $494,000 from our relationship with Altair.

Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Healthcare, a UK-based company that was founded in 2006 by gastrointestinal drug developers to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Healthcare 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 Healthcare in the form of equity. At December 31, 2007, we owned approximately 13% of Atlantic Healthcare's equity. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic Healthcare's request, we will attempt to identify a second-generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate

under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second-generation lead drug candidate. During 2007, we did not recognize any revenue from our relationship with Atlantic Healthcare.

ImQuest Pharmaceuticals, Inc.

In April 2006, we granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, we will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, we are entitled to a portion of the consideration received. During 2007 and 2006, we did not recognize any revenue from our relationship with ImQuest.

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 are used 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, 2007 and 2006, we owned less than 10% of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products. During 2007 and 2006, we did not recognize any revenue from our relationship with Achaogen.

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 consisting of $250,000 in cash and a $250,000 convertible note. iCo 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.

In December 2005, we entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased drug manufactured by us for $700,000. iCo made a $525,000 prepayment to us consisting of $175,000 in cash and a $350,000 convertible note. In December 2006, our obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid us the remaining balance of $175,000. In May 2006, we received 869,025 shares of iCo common stock for the conversion of the convertible notes for the upfront fee and drug we manufactured. iCo's common stock is listed on the TSX Venture Exchange under the stock symbol "ICO". At December 31, 2007, we owned approximately 10% of iCo's equity, compared to less than 10% at December 31, 2006. During 2007, we did not recognize any revenue from our relationship with iCo, compared to $550,000 and $250,000, for 2006 and 2005, respectively.

OncoGenex Technologies 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. We fund 35% of the costs of developing OGX-011. In exchange, we receive 35% of any revenue generated by OncoGenex for OGX-011.

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug. 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, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we further broadened our antisense drug development partnership 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 the preclinical and clinical development of the drugs. 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 also 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, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-427.

During 2007, 2006 and 2005, we earned revenue of $4,000, $1.2 million and $2.7 million, respectively, related to our collaboration with OncoGenex. As of December 31, 2007 and 2006, our ownership interest in OncoGenex was less than 10%.

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 that are 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. This year we added Archemix, focused on aptamer technology, to our technology development satellite company partners which also include Alnylam, working on RNA interference, and Ercole, working on alternative splicing.

Archemix

In August 2007, we and Archemix entered into a new 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 the mRNA-targeting aspect that antisense mechanisms, including RNAi, exploit. 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 that was 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 our drugs. During 2007, we recognized revenue of $250,000 related to the milestone payment we received.

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 developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable 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 either an exclusive or co-exclusive basis depending on the target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million and are payable by us upon the occurrence of specified development and regulatory events. As of December 31, 2007, we did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

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, 2007, we have earned a total of $31.5 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners, including $26.5 million resulting from Alnylam's sublicense of our technology to Roche, which we recognized in the third quarter of 2007.

During 2007, 2006 and 2005, we sold Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2007, we no longer own any shares of Alnylam. During 2007, 2006 and 2005, we generated revenue from our relationship with Alnylam totaling $26.5 million, $750,000 and $3.7 million, respectively, representing 38%, 3% and 9%, 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 includes a cross-license of our respective splicing-related intellectual property with Ercole. We are combining 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 certain of our chemistry patents. Pursuant to the terms of the Note and Warrant Purchase Agreement, during 2003 and early 2004, we made cash payments to Ercole of $500,000 and $250,000, respectively, in exchange for a convertible note. We expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement. We also have the option to make an additional equity investment in Ercole. During 2007,2006 and 2005, 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 instance, our strategic partner Genzyme has preferred access to future Isis drugs for CNS and certain rare diseases. In addition, our ALS and Huntington's Disease programs are supported by external 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 2007 and 2006, we recognized revenue of $329,000 and $70,000, respectively, from our relationship with CHDI.

National Institutes of Health

In September 2007, we received a multi-year Phase 2 SBIR grant by the NIH for up to $1.5 million to design oligonucleotide drugs that can exploit the RNAi antisense mechanism for disease treatment. The Phase 2 grant builds upon a successfully completed Phase 1 program that demonstrated the feasibility of using single-stranded antisense drugs to target the RNAi pathway.

The multi-year grant will fund our research to improve the stability and tissue distribution of RNAi drugs. Much of the work will focus on optimizing the chemical properties of single-stranded oligonucleotides that trigger the RNAi pathway. In addition to demonstrating that compounds optimized with our chemistries produce superior results in animal models when compared to unoptimized compounds, the grant funds the discovery of RNAi-based drugs. During 2007, we recognized revenue of $119,000 related to this grant.

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, ISIS 325568 and ISIS 377131. In this transaction, we licensed to Symphony GenIsis the intellectual property related to our three drug programs, apoB-100, GCGR and GCCR. 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 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. 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 OMI, as part of the collaboration agreement with them, worldwide development and commercialization rights to the two diabetes drugs, ISIS 325568 and ISIS 377131, 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.

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 royalties and modest milestone payments 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 333611.

Intellectual Property Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We own or exclusively license more than 1,500 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 licensing program in which we license aspects of our intellectual property to companies like 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. As of December 31, 2007, we had generated more than $111 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

In May 2001, we entered into an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. 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. In exchange for the license to Hybridon's antisense patents, we paid $15 million in cash and agreed to pay Hybridon $19.5 million in our common stock before May 2003. In return for access to our patents, Hybridon agreed to pay us $6 million in Hybridon common stock before May 2004. During 2004 and 2005, we sold all of our Hybridon stock for net proceeds of approximately $665,000. In September 2005, Hybridon changed its name to Idera Pharmaceuticals, Inc. During each of the years ended December 31, 2007, 2006 and 2005, we earned revenue of $10,000 related to our relationship with Hybridon.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, we expanded this license agreement to allow us to exclusively

sublicense this intellectual property for functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees and will pay royalties on sales of the drugs utilizing the technology IDT licensed to us. During 2007 and 2005, we did not recognize any revenue from our relationship with IDT, compared to $20,000 in 2006.

Out-Licensing Arrangements; Royalty Sharing Agreements

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 associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. 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 2007, 2006 and 2005, 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 Drug Royalty Trust 3. In October 2007, as a resolution for the various alleged competing breaches between us and DRT, DRT paid us $7 million, subject to the terms of an amendment to the original agreement, and an unaffiliated third party paid us $1 million as the final purchase price installment. 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 2007, 2006 and 2005, we recognized revenue of $7 million, $8 million and $7 million, respectively, under this arrangement.

As part of the sale, we agreed to pay DRT liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRT will receive a ten per cent per annum return, compounded quarterly on the total of all purchase price payments made by DRT to us through the default date minus the total of any royalties received by DRT through the default date. To date, DRT has received royalties of $6.4 million. In addition, DRT may withhold any installment of the purchase price if immediately prior to such payment, we fail to meet a minimum liquidity requirement equal to the then outstanding balance on our loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRT has paid the impending purchase price installment; plus its cash burn over the most recent three months. 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 2007, 2006 and 2005, we recognized revenue of $807,000, $200,000 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", "Tuschl IV" and "Esau" patents. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. Thereafter, we and Alnylam will share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. Regulus is operated 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 mutually agreed upon by us and Alnylam.

We transferred to Regulus certain funded research programs that will support Regulus' technology development goals. These programs include a grant from the Israel-U.S. Binational Industrial R&D Foundation, that supports research in the identification of a microRNA therapeutic for the treatment of HCV and a Small Business Innovation Research grant that supports further research for the miR-122 program.

Ibis Collaborations

We developed, within Ibis, the Ibis T5000 Biosensor System with substantial funding from government agencies. In particular, funding from the Defense Advanced Research Projects Agency, or DARPA, of a multi-year collaboration with San Diego-based Science Applications International Corporation, or SAIC, to identify infectious agents in biological weapons attacks made the initial development of the Ibis universal biosensor technology possible. A grant to Ibis from the CDC furthered development and application of our Ibis technology to the surveillance of human infectious disease in the United Sates.

Under these programs, Ibis successfully demonstrated proof-of-principle of its biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. Many of our early government partners are now commercial customers of instruments, assay kits and/or assay services. We continue to work with government collaborators to further develop and expand the applications for the Ibis T5000 Biosensor System. Examples of these ongoing collaborations include:

- Ibis' grant from the National Institutes of Allergy and Infectious Diseases, or NIAID, a division of the NIH, for the development of applications to diagnose infectious diseases;

- Ibis' contract with the Defense Threat Reduction Agency, or DTRA, an agency within the Department of Defense, to advance sample preparation methodologies and validate applications on the Ibis T5000 Biosensor System for broad biological weapon detection;

- Ibis' contract with the NIAID to develop an Ibis T5000 application to specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of

unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates;

- Ibis' subcontract with the University of Maryland School of Medicine to apply the Ibis T5000 technology to identify the causes of diarrheal diseases in developing countries; and

- Ibis' contract with the Department of Homeland Security Science and Technology Directorate, or DHS-S&T, for the advancement of Ibis' microbial forensics applications and the enhancement of Ibis' microbial database.

We are now commercializing the Ibis T5000 instrument, assay kits, and our assay services to both government and non-government customers.

Commercial Agreements

We plan to work with partners to manufacture, install and support Ibis T5000 instruments. In addition, our recent strategic alliance with Abbott provides Ibis with the necessary capital and focus to move quickly toward evolving Ibis toward larger commercial markets, such as clinical diagnostics.

Abbott Molecular Inc.

In January 2008, we, Ibis and Abbott entered into a strategic alliance master agreement pursuant to which:

- Abbott purchased Ibis common stock representing approximately 10.25% of the issued and outstanding common stock of Ibis for a total purchase price of $20 million;

- Ibis granted Abbott a subscription right to purchase an additional $20 million of Ibis common stock before July 31, 2008, which when combined with Abbott's initial investment would represent approximately 18.6% of the issued and outstanding common stock of Ibis;

- We granted Abbott an exclusive call option to acquire from us all remaining Ibis capital stock for a purchase price of $175 million, which, subject to Ibis satisfying a defined set of objectives, may be increased to as much as $190 million;

- If Abbott ultimately acquires Ibis under the call option agreement, Abbott will make the earn out payments described below, which will enable our shareholders to continue to benefit from Ibis' success.

The investment by Abbott provides Ibis the funding to take the key next steps in enhancing its value, while allowing it to remain independent and focused during the option period so as to best enable this progress. This alliance with Abbott also provides Ibis the benefit of an experienced partner in molecular diagnostics and will focus Ibis on commercial success.

If Abbott acquires from us all of the remaining Ibis capital stock under the call option, Abbott will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis T5000 Biosensor Systems, including instruments, assay kits and successor products from the date of the final acquisition through December 31, 2025. These earn out payments will equal 5% of Ibis' cumulative net sales over $150 million and up to $2.1 billion, and 3% of Ibis' cumulative net sales over $2.1 billion. The earn out payments may be reduced from 5% to as low as 2.5% and from 3% to as low as 1.5%, respectively, upon the occurrence of certain events. In addition, as part of the final acquisition, Ibis may distribute to us, immediately prior to the closing, all of Ibis' cash on hand and any receivables or other payments due to Ibis under government contracts and grants held by Ibis as of the closing.

The call option initially expires on December 31, 2008, provided that, subject to certain conditions, Abbott may extend the term of the call option through June 30, 2009. In addition, if Abbott does not exercise its subscription right by July 31, 2008, the call option will expire.

Until the expiration of the call option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis' capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. In addition, the strategic alliance contains a make whole provision such that in the event of a liquidation or change of control of Ibis, Abbott will receive a payment equal to the price paid per share of the capital stock of Ibis acquired by Abbott in the initial investment and under the subscription right, plus a yield of 3% annually from the date Abbott purchased the Ibis common stock, prior to the distribution of any proceeds to any other holders of Ibis capital stock.

Bruker Daltonics Inc.

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Under the agreement, Bruker Daltonics is the exclusive worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations, and service in North America, Europe, and the Middle East. In Europe and the Middle East, Bruker Daltonics will have exclusive rights to sell Ibis T5000 systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. Ibis has maintained worldwide marketing rights to the diagnostics market. By partnering with Bruker Daltonics, our goal was to eliminate the duplication of expenses associated with instrument development, manufacture, sales and service, and gain entry into the market much more rapidly than we could on our own. However, we believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have initiated the formal dispute resolution process under the agreement so that we can improve the manufacture, service and sales of our Ibis T5000 Biosensor Systems. Until we resolve our dispute with Bruker Daltonics, we will manufacture, sell and service our Ibis T5000 Biosensor Systems.

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. For example, in November 2004, we and Nitto Denko Corporation announced that we had jointly developed a new high performance solid support for the manufacture of oligonucleotides.

As part of our relationship with Lilly, in 2002 we upgraded and expanded our manufacturing facility, including the addition of a new state-of-the-art manufacturing suite. Lilly provided us with $21.2 million in funding to build the new suite. 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 will be upgrading and optimizing the efficiency of our manufacturing facility. We plan to begin these upgrades in late 2008.

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, iCo, Lilly and OncoGenex. 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 LLC

Currently, Regulus only requires small quantities of drugs to conduct its drug discovery programs. We are able to 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.

Ibis Biosciences, Inc.

We plan to work with partners to manufacture, install and support Ibis T5000 instruments, while we focus on the high-volume consumables opportunity through manufacturing and sale of the assay kits and related products. In July 2006, Ibis executed a four-year manufacturing and co-marketing agreement with Bruker Daltonics, a subsidiary of Bruker Biosciences Corporation, to build and install the Ibis T5000 Biosensor System and provide ongoing support to customers beginning in 2007. The Ibis T5000 integrates Bruker Daltonic's off-the-shelf microTOF™ instrumentation with Ibis' sample processing technology and microbe database. Under the agreement, Bruker Daltonics is the exclusive worldwide manufacturer of the Ibis T5000 Biosensor System and is also responsible for order processing, system installations, and service in North America, Europe, and the Middle East. By partnering with Bruker Daltonics, our goal was to eliminate the duplication of expenses associated with instrument development, manufacture, sales and service, and gain entry into the market much more rapidly than we could on our own. However, we believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have initiated the formal dispute resolution process under the agreement so that we can improve the manufacture, service and sales of our Ibis T5000 Biosensor Systems. Until we resolve our dispute with Bruker Daltonics, we will manufacture, sell and service our Ibis T5000 Biosensor Systems.

Ibis manufactures and sells high-volume consumables, and has completed building a 1,500 square foot suite dedicated to manufacturing assay kits in its Carlsbad, California facility. We have identified suppliers for raw materials we use to produce quality-controlled ingredients that go into the Ibis T5000 assay kits. Additionally, Ibis has developed quality control and quality assurance standard operating protocols for its assay kits.

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, 2008, we owned or exclusively licensed more than 1,500 issued patents worldwide.

Isis Pharmaceuticals, Inc.

We own or control patents that provide exclusivity for particular products in development and also patents that provide exclusivity to our core technology in the field of antisense more generally. Our core technology patents include claims to oligonucleotides independent of specific cellular target, nucleic acid sequence, or clinical indication. Patents providing exclusivity for a particular product are more narrowly drawn to oligonucleotides having specific nucleic acid sequences and chemical modifications. By obtaining broader core technology patents in addition to more specific product patents, our strategy is to maintain our competitive advantage in the field of antisense technology and have multiple patents covering each potential drug product.

The broadest Isis patents claim nucleoside modifications and oligonucleotides comprising the modified nucleosides. Nucleosides are the basic building blocks of our 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 may rely on different mechanisms of action, including oligonucleotides useful for RNaseH1-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 motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Motif claims are also 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, such as 2'-MOE, and a region comprising deoxyribonucleosides. Oligonucleotides incorporating these motifs are well suited for uses that depend on RNase H1. In fact, the '315 patent claims all of our second generation development candidate antisense compounds until the '315 patent expires in March of 2023, since all of these candidate compounds comprise the claimed motif. Similarly, US Patent Nos. 5,898,031 and 6,107,094, the Crooke Patents, claim oligonucleotides comprising motifs that activate the RNAi pathway. We licensed these patents to Alnylam for double-stranded compounds.

We also own more than 400 patents, worldwide, with claims to antisense oligonucleotides directed to particular clinically 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, U.S. Patent No. 6,261,840 claims a wide range of oligonucleotides targeting PTP-1B, including, but not limited to, chemically modified oligonucleotides. Claims in this patent are not limited to a particular nucleic acid sequence or by nucleoside modification or motif. Likewise, U.S. Patent No. 6,602,857 claims methods of decreasing blood glucose in an animal by administering an antisense compound targeting PTP-1B, regardless of the specific sequence, motif, or modifications of the antisense compound.

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 claim 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, LLC

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 and to specific compounds. For example, U.S. Patent No. 7,232,806 includes claims to antisense compounds targeted to miR-122.

Ibis Biosciences, Inc.

We use the same strategy of seeking patent protection on a broad technology platform as well as specific patents covering our products for our Ibis business as we do for our drug discovery and development business. As a result, Ibis owns or controls patents that protect Ibis' products. For example, Ibis owns patents claiming methods and reagents covering the Ibis T5000 Biosensor System and its use. Ibis patents include claims to kits useful for identifying unknown bioagents, including, but not limited to, bacteria, viruses, fungi and protozoa. For example, US Patent No. 7,108,974, which issued in September 2006, covers the use of the Ibis T5000 to identify unknown bacterial organisms until this patent expires in March 2021.

Competition

Drug Discovery and Development

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.

A number of factors have affected the market for Vitravene, our antisense drug for CMV retinitis. Anti-HIV drugs that were introduced prior to Vitravene's approval 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.

Ibis Biosciences, Inc.

While Ibis has a unique technology, the markets for our technologies and products, including biodefense, forensics, epidemiological surveillance, hospital-associated infection control, and IVD, are very competitive, and we expect the intensity of competition to increase. Currently, we compete primarily with companies that are pursuing technologies and products that provide specific detection of individual pathogens requiring a separate test for each pathogen, as opposed to broad identification and strain determination of infectious agents. We are unaware of other technologies that have the ability to do the parallel analysis, quantification, and identification of the bacteria and viruses in a single sample.

Some of the technologies that the Ibis T5000 competes with, including molecular-based approaches, such as real time PCR, bead based techniques, two dimensional arrays, and PCR amplicon sequencing, are being rapidly adopted as new standards in clinical infectious disease diagnostics, although hospitals still rely heavily on traditional culture methods. Emerging molecular-based approaches for the parallel detection of known infectious agents include multiplexed PCR methods and microarray strategies. With the emerging molecular-based methods, prior knowledge and assumptions about the type and strain of bacteria or virus guide the detection strategies, making them less amenable for the high-throughput detection of a broad spectrum of microorganisms or the detection of previously unknown or uncharacterized agents.

The diagnostics industry is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. In order to achieve market acceptance of our Ibis T5000 Biosensor System, we will be required to demonstrate that it provides accurate, cost-effective and/or time saving alternatives to tests performed by traditional laboratory procedures and products made by our competitors.

Employees

As of March 1, 2008, we employed approximately 300 people. Included in our total number of employees is 62 people within our Ibis 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 March 1, 2008:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D	62	Chairman, Chief Executive Officer and President
B. Lynne Parshall, J.D	52	Director, Chief Operating Officer, Chief Financial Officer and Secretary
Jeffrey M. Jonas, M.D	55	Executive Vice President
C. Frank Bennett, Ph.D	51	Senior Vice President, Antisense Research
David J. Ecker, Ph.D	53	Senior Vice President, Chief Scientific Officer of Ibis Biosciences, Inc.
Michael J. Treble	61	Senior Vice President, President of Ibis Biosciences, Inc.
Kleanthis G. Xanthopoulos, Ph.D	49	Senior Vice President, Chief Executive Officer and President of Regulus Therapeutics LLC

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

Chairman, Chief Executive Officer and President

Dr. Crooke was 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 served as an Executive Vice President prior 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 on the Board of Trustees of the Bishops School and is also 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.

JEFFREY M. JONAS, M.D.

Executive Vice President

Dr. Jonas joined Isis as Executive Vice President in February 2007. He leads Clinical Development, Preclinical Development, Regulatory Affairs, and Quality Assurance and Compliance at Isis. Prior to joining Isis Pharmaceuticals, Dr. Jonas was Chief Medical Officer and Executive Vice President at Forest Laboratories, Inc., where he was responsible for Clinical Development, Medical Affairs, Pharmacovigilence, Regulatory Affairs, Health Economics, and External Scientific Affairs. Dr. Jonas' initial experience in the pharmaceutical industry began in 1991 at Upjohn Laboratories, initially as Director of Psychopharmacology and after several promotions finally as Chief Medical Officer and VP, Clinical Development.

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 as a Director of Antisense Therapeutics Ltd., a biopharmaceutical company.

DAVID J. ECKER, Ph.D.

Senior Vice President, Chief Scientific Officer of Ibis Biosciences, Inc.

Dr. Ecker was promoted to Senior Vice President in January 2008. He was a founder of Isis and has served as a Vice President from June 1995 to January 2008. In 2001, he assumed the role of Scientific Head of our Ibis subsidiary and is currently serving as its Chief Scientific Officer. He served as our Vice President, Biology from July 1993 to June 1995, as our Executive Director, Molecular and Cellular Biology from February 1993 to July 1993, and as our Director, Molecular and Cellular Biology from February 1989 to February 1993. From 1984 until February 1989, he was employed by SmithKline and French Laboratories in a variety of research positions.

MICHAEL J. TREBLE

Senior Vice President, President of Ibis Biosciences, Inc.

Mr. Treble was promoted to Senior Vice President of the Company in January 2008. He joined Isis in December 2004 as President of our Ibis subsidiary and a Vice President of the Company. Prior to joining Isis, Mr. Treble was President and Chief Executive Officer from 2000 to 2003 of Nimblegen Systems, Inc., which develops DNA micro array and chemistry technologies. From 1995 to 2000, Mr. Treble was the Executive Vice President, Chief Operating Officer and Director of Third Wave Technologies, Inc. which provides research and molecular diagnostic products to the healthcare industry. Mr. Treble was also the Chairman, Chief Executive Officer and founder of Genetic Models, Inc. from 1991 until it was sold to Charles River Laboratories in July 2001.

KLEANTHIS G. XANTHOPOULOS, Ph.D.

Senior Vice President, Chief Executive Officer and President of Regulus Therapeutics LLC

Dr. Xanthopoulos joined Isis in December 2007 as President and Chief Executive Officer of Regulus and a Senior Vice President of the Company. Before joining Regulus, Dr. Xanthopoulos was a managing director of Enterprise Partners Venture Capital. Prior to that, he was a co-founder and served as President and Chief Executive Officer and Director of Anadys Pharmaceuticals from its inception in May 2000 to November 2006. From 1997 to 2000, he held a variety of positions at Aurora Biosciences Corporation (now Vertex Pharmaceuticals Incorporated) including Vice President, Genomics & Molecular Biology.
Dr. Xanthopoulos is a member of the board of directors of Anadys Pharmaceuticals Inc., Odyssey Thera, Inc., and an executive board member of BIOCOM, Southern California's life sciences industry association, where he chairs the Capital Formation Committee.

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. In addition to the other information in this report on Form 10-K, you should carefully consider the risks described below before purchasing our securities. 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, 2007, we had accumulated losses of approximately $827.7 million and stockholders' equity of approximately $872,000. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, 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 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 Healthcare, iCo, ImQuest, Lilly, Merck, OncoGenex and OMI. 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, OMI 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, OMI, 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 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.

In addition, our Ibis business relies in part on trade secret laws and nondisclosure, confidentiality and other agreements to protect some of the proprietary technology that is part of the Ibis T5000 Biosensor System. However, these laws and agreements may not be enforceable or may not provide meaningful protection for Ibis' trade secrets or other proprietary information in the event of unauthorized use or disclosure or other breaches of these agreements.

Until recently, virtually all of Ibis' research and development activities have been funded under contracts from the U.S. government (either directly or through subcontracts from prime contractors or higher-tier subcontractors). As a general matter, subject to certain disclosure, notice, filing, acknowledgement and reporting obligations, Ibis is entitled to retain title to any inventions conceived or first reduced to practice under government contracts, but the government will have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced these inventions for or on behalf of the United States.

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. 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. Based on our existing cash and committed cash, including the $175 million mipomersen licensing fee from Genzyme, but not including the up to $210 million we could receive from Abbott, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years. 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;
- success in developing and commercializing a business based on our Ibis T5000 Biosensor System to identify infectious organisms; 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.

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.

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, 2007, the market price of our common stock ranged from $8.30 to $18.23 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 such 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 we cannot be certain that the coverage or coverage limits of our insurance policies will 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 and development facilities, it could delay our progress developing and commercializing our drugs or our Ibis T5000 Biosensor System.

We are developing our Ibis T5000 Biosensor System in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis T5000 Biosensor System and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of 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.

In addition, 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.

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 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. Finally, 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.

The accounting method for our convertible debt securities may be subject to change.

A convertible debt security providing for share and/or cash settlement of the conversion value and meeting specified requirements under EITF Issue No. 00-19, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock*, including our outstanding convertible debt securities, is currently classified in its entirety as debt. No portion of the carrying value of such a security related to the conversion option indexed to the issuer's stock is classified as equity. In addition, interest expense is recognized at the stated coupon rate. The coupon rate of interest for convertible debt securities, including our convertible debt securities, is typically lower than what an issuer would be required to pay for nonconvertible debt with otherwise similar terms.

The EITF recently considered whether the accounting for convertible debt securities that requires or permits settlement in cash either in whole or in part upon conversion, "cash settled convertible debt securities," should be changed, but was unable to reach a consensus and discontinued deliberations on this issue. Subsequently, in July 2007, the FASB voted unanimously to reconsider the current accounting for cash settled convertible debt securities, which includes our outstanding convertible debt securities. In August 2007, the FASB exposed for public comment a proposed FASB Staff Position ("FSP") that would change the method of accounting for such securities and would require the proposed method to be retrospectively applied. The FSP, if issued as proposed, would become effective for calendar year end companies like us in the first quarter of 2009. Under this proposed method of accounting, the debt and equity components of our convertible debt securities would be bifurcated and accounted for separately in a manner that would result in recognizing interest on these securities at effective rates more comparable to what we would have incurred had we issued nonconvertible debt with otherwise similar terms. The equity component of our convertible debt securities would be included in the paid-in-capital section of stockholders' equity on our balance sheet and, accordingly, the initial carrying values of these debt securities would be reduced. Our net income for financial reporting purposes would be reduced by recognizing the accretion of the reduced carrying values of our convertible debt securities to their face amounts as additional non-cash interest expense. Therefore, if

the proposed method of accounting for cash settled convertible debt securities is adopted by the FASB as described above, it would have an adverse impact on our past and future reported financial results.

We cannot predict the outcome of the proposed FSP. We also cannot predict any other changes in GAAP that may be made affecting accounting for convertible debt securities, some of which could have an adverse impact on our past or future reported financial results.

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, if approved for commercialization, doctors will 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 or result in FDA enforcement action after approval that could limit the commercial success of our potential products.

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; or
- more effective 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 our joint venture with Alnylam focused 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 managing board comprised of an equal number of directors appointed by each of Alnylam and us. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by the managing board. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' managing 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.

Risks Associated With Our Ibis Biosciences Business

We may not successfully develop or derive revenues from our business based on our Ibis T5000 Biosensor System.

Our Ibis T5000 Biosensor System is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires continued research and development to achieve our business objectives. For Ibis to be commercially successful, we must convince potential customers that our Ibis T5000 Biosensor System is an attractive alternative to existing methods of identifying pathogens. If our potential customers fail to purchase our Ibis T5000 Biosensor System due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we may not recover our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

If we fail to sell the Ibis T5000 Biosensor System to a minimum customer base, our ability to generate revenues from sales of assay kits will be negatively affected.

A key element of our business plan for Ibis calls for us to deploy the Ibis T5000 Biosensor System to a broad customer base. If we cannot create a broad installed base of our Ibis T5000 Biosensor System, our ability to sell assay kits, the consumables used to operate the system, may be significantly and adversely affected. Even if we successfully achieve broad installation of the Ibis T5000 Biosensor System, customers may not perform as many analyses as we anticipate, which may affect the assumptions underlying our business plan for Ibis and lead to lower-than-expected revenues.

We will depend on Bruker Daltonics to manufacture the Ibis T5000 Biosensor System and any failure of Bruker Daltonics to fulfill its obligations could harm or delay our commercialization efforts.

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker Daltonics will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. As such, we rely heavily on Bruker Daltonics to successfully manufacture, distribute and service our Ibis T5000 Biosensor System, but do not control many aspects of Bruker Daltonics activities. We believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have initiated the formal dispute resolution process under the agreement so that we can improve the manufacture, service and sales of our Ibis T5000 Biosensor Systems. If Bruker Daltonics continues to fail to carry out its obligations under our alliance, its failure could harm or delay the commercialization of our Ibis T5000 Biosensor System.

Ibis' strategic alliance with Abbott may restrict the way Ibis conducts its business and may not result in the ultimate sale of Ibis to Abbott.

On January 30, 2008, we and Ibis entered into a Strategic Alliance Master Agreement with Abbott. As part of this transaction, we granted Abbott an exclusive option to acquire from us all remaining Ibis capital stock. Under the exclusive option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. These consent requirements may restrict the way Ibis conducts its business and may discourage others from trying to collaborate with or buy our Ibis subsidiary. Abbott's decision to exercise the exclusive option is at its sole discretion. As a result, we cannot guarantee that Abbott will exercise its option to acquire the remaining Ibis capital stock. If Abbott does not exercise its option to acquire the remaining Ibis capital stock, we will not realize the full benefit of the strategic alliance and we may need to secure a new partner to further expand the Ibis business into the areas of hospital associated infection control and infectious disease diagnostics.

We depend on government contracts for most of Ibis' revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows.

Historically, most of Ibis' revenues were from the sale of services and products to the U.S. government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, even if we have fully performed our obligations. Since a large portion of Ibis' government contracts are milestone based, if Ibis fails to meet a specific milestone within the specified delivery date, our government partner may be more likely to reduce or cancel its contract with Ibis. Our revenues and cash flows from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months and year ended December 31, 2007, we derived approximately 13% and 16%, respectively, of our revenue from agencies of the U.S. government. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

If U.S. defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

We may be liable for penalties under a variety of procurement rules and regulations, and changes in government regulations could adversely impact our revenues, operating expenses and operating margins.

Under our agreements with the U.S. government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and we do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of Ibis. With respect to U.S. government contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with the U.S. government. Among the most significant regulations are the following:

- the U.S. Federal Acquisition Regulations, which comprehensively regulate the formation, administration and performance of government contracts;
- the U.S. Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with contract negotiations; and
- the U.S. Cost Accounting Standards, which impose accounting requirements that govern our right to reimbursement under certain cost-based government contracts.

If our Ibis T5000 Biosensor System's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex instruments such as our Ibis T5000 Biosensor System typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 Biosensor System and its related applications, we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

If we had to replace a supplier of one of the major hardware components of our Ibis T5000 Biosensor System, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our Ibis T5000 Biosensor System. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle. For example, Bruker Daltonics supplies the mass spectrometer we use as part of our Ibis T5000 Biosensor System.

If Ibis fails to compete effectively, it may not succeed or contribute significant revenues.

The market for products such as Ibis' is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. To remain competitive, we will need to continually improve Ibis' products so that, when compared to alternatives, its products:

- provide faster results;
- are cost-effective;

- deliver more accurate information;
- are more user friendly; and
- support a broad range of applications.

If Ibis cannot keep its products ahead of its competitors in these areas, Ibis' revenues will suffer and we may not meet our commercialization goals.

Many of Ibis' competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than Ibis. Moreover, these companies may have substantially greater expertise in conducting clinical trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than Ibis. In addition, Ibis' competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than Ibis.

Improvements in preventing major diseases could reduce the need for our Ibis T5000 Biosensor System and related assay kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our Ibis revenues from the sale of assay kits necessary to use our Ibis T5000 Biosensor System. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our assay kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our assay kits, which could reduce our revenues.

Our plans to commercialize the Ibis T5000 Biosensor System internationally are subject to additional risks that could negatively affect our operating results.

Our success will depend in part on our ability and Bruker Daltonics' ability to market and sell the Ibis T5000 Biosensor System and assay kits in foreign markets. Expanding our international operations could impose substantial burdens on our resources, divert management's attention from domestic operations and otherwise adversely affect our business. Furthermore, international operations are subject to several inherent risks including:

- trade protective measures and import or export licensing requirements or other restrictive actions by U.S. and foreign governments could prevent or limit our international sales;
- reduced protection of intellectual property rights;
- changes in foreign currency exchange rates;
- changes in specific country's or region's political or economic conditions; and
- changes in tax laws.

If we cannot access or license rights to particular nucleic acid sequences for targeted diseases in the future, we may be limited in our ability to develop new products and access new markets.

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially

reasonable terms or at all, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our Ibis T5000 Biosensor Systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis T5000 Biosensor Systems or services.

The sales cycles for Ibis T5000 Biosensor Systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

If we or our partners are required to obtain regulatory approval for our Ibis T5000 Biosensor System, we may not successfully obtain approval.

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, and uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of clinical trials do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

If we become subject to product liability claims relating to Ibis, we may be required to pay damages that exceed our insurance coverage.

Any product liability claim brought against us with respect to Ibis, with or without merit, could result in the increase of our product liability insurance rates or the inability to secure coverage in the future. Expenses incurred by our insurance provider in defending these claims will reduce funds available to settle claims or pay adverse judgments. In addition, we could be liable for amounts in excess of policy limits, which would have to be paid out of our cash reserves, and our cash reserves may be insufficient to satisfy the liability. Finally, even a meritless or unsuccessful product liability claim could harm Ibis' reputation in the industry, lead to significant legal fees, and could result in the diversion of management's attention from managing our business.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of March 1, 2008, we occupied approximately 130,600 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, and 12,900 square feet, which our Ibis subsidiary occupies, including 1,500 square feet of manufacturing area for Ibis' assay kits. We are located in three buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The lease for the building that houses our Ibis business will expire in 2010 and has two five-year options to extend the lease. The lease on the building we primarily use for laboratory and office space for our drug development business will expire in 2012 and has a five-year option to extend the lease. The lease on the building we primarily use for our drug development manufacturing will expire in 2020 and has two five-year options to extend the lease.

Subsequent to March 1, 2008, we entered into a lease for additional office and lab space for our drug development business. Initially, we will occupy approximately 9,500 square feet and in the second half of 2008, we will increase the space we occupy to approximately 23,700 square feet. The lease for this space expires in 2011 and has two five-year options to extend the lease.

Item 3. Legal Proceedings

On October 16, 2007, Idera Pharmaceuticals, Inc. (formerly Hybridon, Inc.) filed papers initiating an arbitration proceeding against us. Idera alleged that we improperly sublicensed certain Idera patents which were the subject of a Collaboration and License Agreement by and between Hybridon, Inc. and us dated May 25, 2001. This matter was arbitrated on December 4, 5 and 6, 2007. The arbitrator entered a final award on January 15, 2008 finding that we "acted wholly within our rights under the agreement in granting a sublicense to Alnylam." We have prevailed and this matter is closed.

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 have 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 have failed to achieve resolution of this dispute. Formal mediation efforts will be pursued immediately in an effort to avoid litigation.

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

Not applicable.

PART II

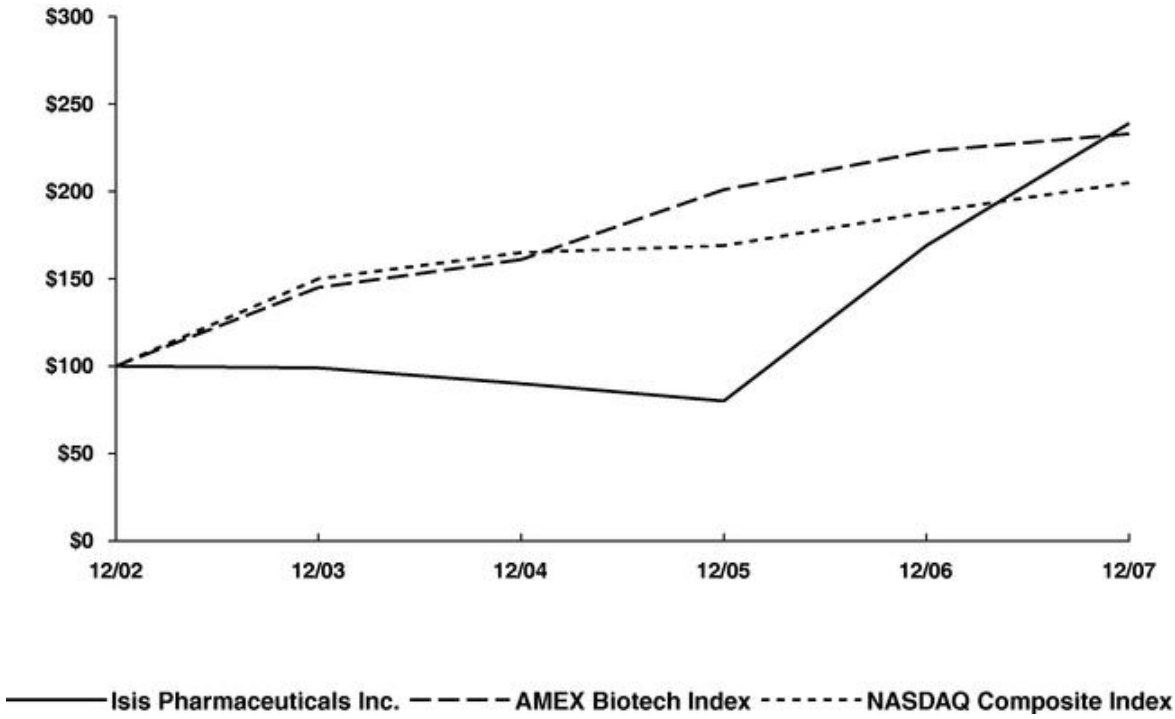
Item 5. Market for Registrant's Common Equity and Related Stockholder Matters and Issuer Repurchases of Equity Securities

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
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
2006		
First Quarter	$ 9.34	$ 5.09
Second Quarter	$ 9.50	$ 5.76
Third Quarter	$ 7.89	$ 5.57
Fourth Quarter	$ 14.00	$ 7.06

As of March 6, 2008, there were approximately 890 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, 2002 in our common stock, the NASDAQ Composite Index (total return) and the AMEX Biotech Index. The total return assumes reinvestment of dividends.



	Dec-02	Dec-03	Dec-04	Dec-05	Dec-06	Dec-07
Isis Pharmaceuticals Inc.	$ 100	$ 99	$ 90	$ 80	$ 169	$ 239
AMEX Biotech Index	$ 100	$ 145	$ 161	$ 201	$ 223	$ 233
NASDAQ Composite Index	$ 100	$ 150	$ 165	$ 169	$ 188	$ 205

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

	Years Ended December 31,				
	2007	2006	2005	2004	2003
Consolidated Statement of Operations Data:					
Revenue	$ 69,621	$ 24,532	$ 40,133	$ 42,624	$ 49,990
Research and development expenses	$ 92,641	$ 80,567	$ 82,467	$ 118,474	$ 116,963
Net loss(1)	$ (10,994)	$ (45,903)	$ (72,401)	$ (142,503)	$ (94,996)
Net loss applicable to common stock(2)	$ (136,305)	$ (45,903)	$ (72,401)	$ (142,864)	$ (95,690)
Basic and diluted net loss per share(2)	$ (1.63)	$ (0.62)	$ (1.15)	$ (2.52)	$ (1.73)
Shares used in computing basic and diluted net loss per share	83,739	74,308	62,877	56,642	55,463

	As of December 31,				
	2007	2006	2005	2004	2003
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 193,719	$ 193,333	$ 94,389	$ 103,883	$ 215,504
Working capital	$ 145,112	$ 181,064	$ 82,065	$ 82,193	$ 194,004
Total assets	$ 258,858	$ 255,907	$ 166,373	$ 208,425	$ 334,942
Long-term debt, capital lease and other obligations, less current portion	$ 186,410	$ 132,866	$ 139,915	$ 236,611	$ 213,397
Noncontrolling interest in Symphony GenIsis, Inc	$ —	$ 29,339	$ —	$ —	$ —
Noncontrolling interest in Regulus Therapeutics LLC	$ 9,371	$ —	$ —	$ —	$ —
Accumulated deficit	$ (827,745)	$ (816,751)	$ (770,848)	$ (698,447)	$ (555,583)
Stockholders' equity (deficit)	$ 872	$ 68,563	$ 2,665	$ (72,133)	$ 67,178

(1) Our net loss includes charges (benefit) related to restructuring activities of ($536,000), $7.0 million, $32.4 million and $1.8 million in 2006, 2005, 2004 and 2003, respectively.

(2) Our net loss applicable to common stock and our basic and diluted net loss per share calculation include $125.3 million excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis in 2007 and accretion of dividends on preferred stock of $361,000 and $694,000 in 2004 and 2003, respectively.

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

Overview

We are a leading company in antisense technology exploiting a novel drug discovery platform to create a broad pipeline of first-in-class drugs. Through our highly efficient and prolific drug discovery platform, we can expand our drug pipeline and our partner's drug 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 conduct early development on these drugs to key value inflection points. Because we can discover more drugs than we can develop, our plan is to discover new drugs, outlicense our drugs to partners and build a growing annuity of milestone payments and royalty income. In this way, we maximize the value of the drugs we discover by licensing our drugs to partners at key development points, which allows us to focus on utilizing our antisense technology platform to discover new drugs. At the same time, we benefit from our partner's expertise to develop, commercialize and market our drugs. For example, we partner our drugs with leading pharmaceutical companies, such as BMS, Genzyme, Lilly and OMI as well as with smaller satellite companies that have expertise in specific disease areas. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam, Ercole and most recently, with Regulus, our joint venture created to focus on microRNA therapeutics. We explore the technology beyond antisense with additional opportunities in infectious disease identification through our Ibis subsidiary and in the discovery and development of aminoglycoside and aptamer drugs through our technology partners, Achaogen and Archemix, respectively. 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 and vast patent estate of more than 1,500 issued patents. We remain one of the largest patent holders in the U.S., and with our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology, our drugs, and the Ibis T5000 Biosensor System—they also form the basis for lucrative licensing and partnering arrangements. We have

generated more than $111 million from our intellectual property licensing program that helps support our internal drug discovery and development programs, included in this amount is the $26.5 million we received in the third quarter of 2007 from Alnylam resulting from Alnylam's sublicense of our technology to Roche.

In addition to the important progress we and our partners made with our second generation drugs in development and the achievements of our Ibis subsidiary in commercializing the Ibis T500 Biosensor System, in 2007 and early 2008, we completed several transactions that significantly strengthened our financial position. In 2007, we issued $162.5 million of $2^{5}/_{8}$% convertible subordinated notes and added two major pharmaceutical partners with our collaborations with BMS and OMI. Additionally in the third quarter of 2007, we received the $26.5 million sublicensing fee from Alnylam's transaction with Roche. Most recently, in January 2008, we entered into a major strategic alliance with Genzyme. These partnerships in combination with additional partnership activity in 2007 and early 2008 have provided us with an aggregate of nearly $450 million in cash payments and the potential to earn over $1.9 billion in milestone payments. These transactions represent the value that we are realizing from our extensive product pipeline and the successes of our partnering strategy, and provide us with the financial strength to continue to successfully execute our goals.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development—Within our primary business segment, we are exploiting a novel drug discovery platform to create a broad pipeline of first-in-class drugs for our drug pipeline and our partners' drug pipelines. Our proprietary technology enables us to rapidly identify, 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 selecting the best drugs. The 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 18 drugs in development. Our partners are licensed to develop, with our support, 15 of these 18 drugs, which substantially reduces our development costs. We focus our internal drug development programs on drugs to treat cardiovascular, metabolic and inflammatory diseases. Our partners focus on disease areas such as ocular, viral, inflammatory and neurodegenerative diseases, and cancer.

Ibis Biosciences, Inc.—Ibis, formerly a wholly owned subsidiary of Isis and now a majority- owned subsidiary of Isis, has developed and is commercializing its biosensor technology, including the Ibis T5000 Biosensor System and assay kits. Ibis' T5000 offers a unique solution for rapid identification and characterization of infectious agents. It can identify virtually all bacteria, viruses and fungi and provide information about drug resistance, virulence and strain type of these pathogens within several hours. Ibis is developing, manufacturing and selling the Ibis T5000 instruments along with the Ibis T5000 assay kits and consumables. Currently we are selling research use only kits for many applications. Examples of these kits include influenza surveillance, *Staphylococcus aureus* genotyping and characterization, antibiotic resistance determination and anthrax genotyping. We continue to develop new kits, and as defined through our agreement with Abbott, we are particularly focused on developing those applications that will be of highest commercial value for the clinical diagnostics market.

Much of the development of the Ibis T5000 Biosensor System and related applications has been funded through government contracts and grants. As of December 31, 2007, we had earned $67.8 million in revenue under our government contracts and grants, and we had an additional $8.3 million committed under our existing contracts and grants.

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. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. 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 marketable 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 billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the consolidated balance sheet.

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. Should different estimates prevail, revenue recognized could be materially different. To date our estimates have not required material adjustments. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, BMS, Lilly, OncoGenex, OMI and Pfizer. Our collaborative agreements typically include a research and/or development project plan that includes activities to be performed 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 date 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, as defined by 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 are not obligated for future performance related to the achievement of the milestone. To date, we have earned milestone payments totaling $1.2 million under our Pfizer collaboration. In January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment and in December 2006, Merck initiated clinical trials of a drug for HCV for which we earned a $1 million milestone payment. Additionally, in September 2007, we earned a $5 million milestone payment for the initiation of a Phase 1 trial for ISIS 325568 under our recently announced collaboration with OMI. Since the milestone was achieved before the contract was finalized, the $5 million is treated as an upfront licensing fee and is amortized over the two year period of our performance obligation.

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 the provisions in SAB 104 were met before we recognized the related revenue.

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

In the fourth quarter of 2006, we started to sell the Ibis T5000 Biosensor System commercially. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since we had no previous experience commercially selling the Ibis T5000 Biosensor System, we had no basis to determine the fair values of the various elements included in each system; therefore, we account for the entire system as one deliverable and recognize revenue over the entire period of performance. The assay kits, which are sold separately from the instrument, are considered part of the entire system from an accounting perspective because the assay kits and the instrument are dependent on each other. For a one-year period following the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System; therefore, we are amortizing the revenue for the entire system, including related assay kits, over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

As part of our Lilly alliance, in 2001 Lilly provided us a $100 million interest free loan to fund the companies' research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, we converted the loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration.

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 marketable securities at fair market value based upon market prices quoted 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.

In addition to our investments in marketable securities, we 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. Unrealized gains and losses related to temporary declines are recorded as a separate component of stockholders' equity. 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 2007, we sold the remaining 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 on investment of $465,000 related to the other-than-temporary impairment of our equity investment in ATL. Since the impairment in the second quarter of 2006, we have recorded a net unrealized gain of $531,000 related to our equity investment in ATL as a separate component of stockholders' equity, reflecting the increase in the market value of the investment since the impairment. We determined that there were no other-than-temporary declines in value of investments in 2007 and 2005.

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 of applications being issued and the scope of our issued patents.

We recorded a charge of $896,000, $2.4 million and $15.6 million for 2007, 2006 and 2005, respectively, primarily related to 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 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. Each of our raw materials can be used in multiple products and, as a result, have future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug could be used to manufacture our other drugs. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. Also included in inventory are material costs and related manufacturing costs associated with our Ibis T5000 Biosensor System and related assay kits. 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 considered 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 unbilled 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 our net deferred tax assets will more likely

than not be recovered 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 Ibis subsidiary based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of 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.

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. SFAS 123R supersedes our previous accounting under Accounting Principles Board Opinion ("APB") 25, *Accounting for Stock Issued to Employees and SFAS 123, Accounting for Stock-Based Compensation*, beginning January 1, 2006. 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.

We adopted SFAS 123R using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Consolidated Statements of Operations for 2007 and 2006 reflect the impact of SFAS 123R. In accordance with the modified prospective transition method, our Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123R. As of December 31, 2007, there was $9.8 million of total unrecognized compensation cost related to non-vested options under stock-based compensation plans. Total unrecognized compensation cost will be adjusted 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 4 for estimating the fair value of the stock-based awards we granted. Compensation expense for all stock-based payment awards is recognized 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. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based 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 they are expected to be outstanding. For our 2002 Non-Employee Directors' Stock Option Plan, we estimate the expected term of options granted based on historical exercise patterns. For our employee stock option plans, the estimated expected term is 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 2007 and 2006. For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information as required under SFAS 123.

We record stock options granted to non-employees at their fair value in accordance with the requirements of SFAS 123, *Accounting for Stock-Based Compensation*, 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, 2007 and December 31, 2006

Revenue

Total revenue for the year ended December 31, 2007 was $69.6 million, compared to $24.5 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 OMI, which began in September 2007.

Period to period fluctuations in revenue are common for us as our revenue is significantly effected by the nature and timing of payments under agreements with our partners, including license fees, and milestone-related payments, such as the $26.5 million we received from Alnylam.

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

	Year Ended December 31,	
	2007	2006
Drug Discovery and Development:		
Research and development revenue	$ 22,319	$ 5,418
Licensing and royalty revenue	36,025	9,441
	$ 58,344	$ 14,859
Ibis Biosciences:		
Research and development revenue	$ 7,765	$ 9,117
Commercial revenue(1)	3,512	556
	$ 11,277	$ 9,673
Total revenue:		
Research and development revenue	$ 30,084	$ 14,535
Commercial revenue(1)	3,512	556
Licensing and royalty revenue	36,025	9,441
	$ 69,621	$ 24,532

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' Consolidated Statements of Operations.

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 OMI offset by a decrease in revenue associated with our collaborations with Lilly and OncoGenex.

In connection with our recently announced strategic relationship with Genzyme, we will amortize the upfront payments from Genzyme into research and development revenue over our period of performance under the collaboration. As a result, we expect our research and development revenue to significantly increase in 2008.

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.

Ibis Biosciences, Inc.

Ibis' revenue for the year ended December 31, 2007 was $11.3 million, compared to $9.7 million for 2006. Ibis earned commercial revenue of $3.5 million for the year ended December 31, 2007, compared to $556,000 for 2006, which consisted of revenue from sales of Ibis T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for each instrument and assay kits over the period of this support obligation. Primarily as a result of the increased number of T5000 Biosensor System placements in 2007, commercial revenue in 2007 was substantially higher than in 2006. In addition, Ibis generated revenue from its government contracts and grants of $7.8 million for the year ended December 31, 2007 compared to $9.1 million for 2006. As Ibis has matured from the research and development stage to the commercial stage, some of its large government contracts that supported technology development have been successfully completed leading to a transient decline in contract revenue for the year ended December 31, 2007. In general, new Ibis contracts support diverse applications of the Ibis T5000 Biosensor System, which benefits not only the government contracting agency, but also Ibis' non-government commercial customers. In addition to its ongoing government contracts, Ibis has recently been granted contracts worth up to $2.8 million. We expect that government contracts will continue to provide a solid revenue base going forward.

From inception through December 31, 2007, Ibis has earned $67.8 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $8.3 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. These agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

In 2007, as our drugs advanced into and through development, we expanded our clinical development programs. Additionally, we built the manufacturing, marketing and sales infrastructure required to successfully commercialize the Ibis T5000 Biosensor System. These activities led to an increase in operating expenses for 2007 compared to 2006. Operating expenses for the year ended December 31, 2007 were $108.6 million, compared to $92.7 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 $9.9 million for the year ended December 31, 2007, compared to $5.7 million for 2006, primarily reflecting the significant increase in our stock price from period to period.

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

	December 31,	
	2007	2006
Drug Discovery and Development	$ 86,487	$ 76,573
Ibis Biosciences	22,082	16,613
Corporate	—	(536)
Total operating expenses	$ 108,569	$ 92,650

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 and costs associated with restructuring activities, which are not part of ongoing operations. We believe these items are not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding them.

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 Ibis subsidiary's research and development expenses, which are discussed in a separate section below. The following table sets forth information on research and development costs (in thousands):

	December 31,	
	2007	2006
Research and development expenses	$ 84,721	$ 76,026
Non-cash compensation expense related to stock options	7,920	4,541
Total research and development as reported	$ 92,641	$ 80,567

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

	December 31,	
	2007	2006
Drug Discovery and Development	$ 75,477	$ 66,893
Ibis Biosciences	17,164	13,674
Total research and development expenses	$ 92,641	$ 80,567

For the year ended December 31, 2007, we incurred total research and development expenses, excluding stock compensation, of $84.7 million, compared to $76.0 million for 2006. The increase is attributable to the expansion of our key programs and the additional costs required to commercialize the Ibis T5000 Biosensor System. Expenses related to Ibis are discussed in a separate section below.

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.

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. We anticipate antisense drug discovery costs to increase in the near-term due to our planned investment to fill our pipeline, initiatives aimed at reducing our costs to manufacture our drugs, additional spending to support collaborative research efforts, along with research efforts conducted by Regulus, which are consolidated into our financial results.

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):

	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. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We are currently conducting multiple Phase 2 trials for mipomersen and recently we initiated a Phase 3 program for mipomersen in patients with familial hypercholesterolemia, 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.

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 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 18 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we have committed to spend $75 million over the next few years to advance the development of mipomersen.

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. 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. 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. 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. We anticipate that our manufacturing and operations costs will increase in 2008 as we continue to expand our key programs and manufacture additional drug supplies for our corporate partners.

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):

	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 were abandoned and written-off during 2006.

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

	December 31,	
	2007	2006
Drug Discovery and Development	$ 18,059	$ 18,998
Ibis Biosciences	2,727	2,518
Total R&D support costs	$ 20,786	$ 21,516

Selling, General and Administrative Expenses

Selling, 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 Ibis sales and marketing. Additionally, we include in selling, 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 the acquisition of Symphony GenIsis in September 2007, selling, general and administrative expenses also included Symphony GenIsis' general and administrative expenses.

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

	December 31,	
	2007	2006
Selling, general and administrative expenses	$ 13,938	$ 11,413
Non-cash compensation expense related to stock options	1,990	1,206
Total selling, general and administrative as reported	$ 15,928	$ 12,619

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

	December 31,	
	2007	2006
Drug Discovery and Development	$ 11,009	$ 9,680
Ibis Biosciences	4,919	2,939
Total selling, general and administrative expenses	$ 15,928	$ 12,619

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2007 were $13.9 million, compared to $11.4 million for 2006. The increase in our drug discovery and development segment 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. The increase in the Ibis segment was primarily the result of increased selling, general and administrative expenses associated with the commercialization of the Ibis T5000 Biosensor System. Expenses related to Ibis are discussed in a separate section below.

Ibis Biosciences, Inc.

Ibis' operating expenses include research and development expenses and selling, general and administrative expenses. Ibis' research and development expenses are primarily the result of its performance under government contracts in support of the ongoing development of the Ibis T5000

Biosensor System and related assay kits. Ibis' expenses include all contract-related costs it incurs on behalf of government agencies in connection with the performance of its obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of the Ibis T5000 Biosensor System. Also included in Ibis research and development expenses are cost of goods sold for its commercial activity. Further, we allocate a portion of R&D support costs to Ibis and include this allocation in Ibis' research and development expenses. Ibis' selling, general and administrative expenses include outside costs in the areas of business development, human resources, and finance that we allocate to Ibis. In addition, corporate expenses required to support Ibis are allocated to Ibis' selling, general and administrative expenses.

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

	December 31,	
	2007	2006
Cost of goods sold	$ 2,705	$ 427
Research and development costs	10,556	9,983
R&D support costs	2,727	2,518
Selling, general and administrative expenses	4,482	2,702
Non-cash compensation expense related to stock options	1,612	983
Total Ibis' operating expenses	$ 22,082	$ 16,613

Ibis' operating expenses, excluding non-cash compensation expense related to stock options, were $20.5 million and $15.6 million for the years ended December 31, 2007 and 2006, respectively. The increase in expenses primarily reflects an increase in costs necessary to support commercialization of the Ibis T5000 Biosensor System. We expect costs and expenses for Ibis to increase as we continue to expand this business and work to achieve the pre-negotiated development milestones established in conjunction with Abbott's investment and purchase option.

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.

Regulus Therapeutics LLC

In September 2007, we and Alnylam formed Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Under accounting rules, we are considered the primary beneficiary of Regulus and consolidate the financial results of Regulus. As a result, our consolidated financial statements include the $10 million of cash contributed by Alnylam to fund Regulus. Our consolidated financial statements also include a line item called "Noncontrolling Interest in Regulus Therapeutics LLC." On our Consolidated Balance Sheet, this line reflects Alnylam's minority ownership of Regulus' equity. As the joint venture progresses, this line item will be reduced by Alnylam's share of Regulus' net losses, which were $629,000 in 2007, until the balance becomes zero. The reductions to the Noncontrolling Interest in Regulus will be reflected in our Consolidated

Statement of Operations using a similar line item and will provide a positive adjustment to our net income (loss) equal to Alnylam's share of Regulus' losses.

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 OMI 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 is 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 a gain realized on the sale of the remaining equity securities of Alnylam that we owned compared to the 2006 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 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. The significantly lower interest rate of the $2^{5}/_{8}$% notes reduces our cash interest payments by approximately $2.6 million per year. In addition, the extended maturity date of the $2^{5}/_{8}$% notes further strengthens our financial position. 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

Net loss for the year ended December 31, 2007 was $11.0 million compared to $45.9 million for 2006. 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, related to our collaboration with Symphony GenIsis and a benefit of $629,000 in the loss attributed to noncontrolling interest in Regulus for 2007. In addition, 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.

Net Loss Applicable to Common Stock

Our improved financial position supported the early purchase in September 2007 of Symphony GenIsis, saving us roughly $75 million over the lifetime of the transaction. 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. 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, 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 California tax loss carryforwards and our research credit carryforwards began expiring in 2005 and 2006, respectively, unless utilized. 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, 2006 and December 31, 2005

Revenue

Total revenue for the year ended December 31, 2006 was $24.5 million, compared to $40.1 million for 2005. The decrease in revenue for 2006 compared to 2005 was primarily due to a decrease in revenue associated with our collaboration with Lilly. This ongoing collaboration was extended in August 2005 to focus on a select number of targets and as a result is no longer a source of significant revenue. Our revenue fluctuates based on the timing of activities under agreements with our partners. For example, we earned revenue in 2006 of $750,000 compared to revenue of $3.7 million in 2005 from Alnylam when it sublicensed our technology to pharmaceutical partners for the development of RNAi therapeutics. In 2006 and 2005, in accordance with agreed upon timing, we also earned $8.0 million and $7.0 million, respectively, of revenue from Drug Royalty USA, Inc., as partial payment for the acquisition of a part of our royalty rights in Macugen. In addition, our Ibis revenue was lower in 2006 than in 2005 as described below under "Ibis Biosciences, Inc."

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

	Year Ended December 31,	
	2006	2005
Drug Discovery and Development:		
Research and development revenue	$ 5,418	$ 16,817
Licensing and royalty revenue	9,441	11,523
	$ 14,859	$ 28,340
Ibis Biosciences:		
Research and development revenue	$ 9,117	$ 11,793
Commercial revenue(1)	556	—
	$ 9,673	$ 11,793
Total revenue:		
Research and development revenue	$ 14,535	$ 28,610
Commercial revenue(1)	556	—
Licensing and royalty revenue	9,441	11,523
	$ 24,532	$ 40,133

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' Consolidated Statements of Operations.

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. Our revenue under the category of research and development revenue under collaborative agreements for the year ended December 31, 2006 was $5.4 million, compared to $16.8 million for 2005. The decrease of $11.4 million was primarily due to a decrease in revenue associated with our collaboration with Lilly.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $9.4 million for the year ended December 31, 2006, compared to $11.5 million for 2005. We earned revenue in 2006 of $750,000 and revenue of $3.7 million in 2005 from Alnylam when Alnylam sublicensed our technology to pharmaceutical partners for the development of RNAi therapeutics. In addition, in 2006 and 2005, in accordance with agreed upon timing, we earned $8.0 million and $7.0 million, respectively, from Drug Royalty USA, Inc., as partial payment for the acquisition of a part of our royalty rights in Macugen.

Ibis Biosciences, Inc.

During 2006, Ibis achieved important milestones in implementing its commercial plan, including receiving its first commercial order for two Ibis T5000 Biosensor Systems, one of which was delivered in late 2006 and the second of which Ibis delivered in early 2007. Additionally, in 2006, Ibis received a contract worth up to $1.9 million to analyze samples in its assay services laboratory. As a result of these achievements, Ibis earned commercial revenue of $556,000 in 2006.

To develop the Ibis T5000 Biosensor System and related assay kits, Ibis receives contracts and grants from U.S. government agencies. Ibis generated revenue from its government contracts and grants of $9.1 million for 2006 compared to $11.8 million for 2005. Ibis' revenue from government contracts fluctuates based on when the contracts are awarded, the period of performance for the contracts, the funding amount of the contracts, the labor rates applicable to the activities under the contracts and the timing and type of these activities. For example, in 2006, two large government contracts that were active in 2005 ended and were replaced with several new but smaller contracts, resulting in reduced revenue in 2006 compared to 2005. Additionally, the average labor rate that Ibis charged its government partners in 2006 was lower than in 2005, which also contributed to Ibis' reduced revenue in 2006 compared to 2005.

We receive our funding from DARPA through a subcontract SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 8% and 14% of our total revenue in the years ended 2006 and 2005, respectively, which represented 20% and 48% of our 2006 and 2005 Ibis revenue, respectively.

Operating Expenses

Total operating expenses were $92.7 million and $97.3 million for the years ended December 31, 2006 and 2005, respectively. The decrease in operating expenses, which was principally a result of cost savings achieved through the increased focus on our key programs, led to a decrease of $4.6 million in our operating expenses in 2006, which included compensation related to stock options for 2006 of $5.7 million and a benefit related to the variable accounting of stock options of $544,000 in 2005. Excluding these two non-cash items related to stock options, our operating expenses were $10.8 million, or 11%, lower in 2006 than in 2005, primarily due to decreases in expenditures in 2006 following our 2005 restructuring.

In order to analyze and compare our results of operations to similar companies, we believe that it is important to exclude non-cash compensation related to stock options and costs associated with restructuring activities, which are not part of ongoing operations. We believe these items are not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding these items.

Research and Development Expenses

For the year ended December 31, 2006, our total research and development expenses were $80.6 million, compared to $82.5 million for the same period in 2005. The decrease of $1.9 million from 2005 to 2006 was primarily due to cost savings achieved as a result of our focus on key programs. Our total R&D expenses in 2006 included compensation expense associated with stock options of $4.5 million. Excluding this non-cash item, our total R&D expenses decreased by $6.4 million, or 8% in 2006 compared to 2005.

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

	December 31,	
	2006	2005
Research and development expenses	$ 76,026	$ 82,467
Non-cash compensation expense related to stock options	4,541	—
Total research and development as reported	$ 80,567	$ 82,467

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

	December 31,	
	2006	2005
Drug Discovery and Development	$ 66,893	$ 69,536
Ibis Biosciences	13,674	12,931
Total research and development expenses	$ 80,567	$ 82,467

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.

Antisense drug discovery costs for the year ended December 31, 2006 were $14.5 million, compared to $17.9 million for 2005. The decrease of $3.4 million from 2005 to 2006 was principally the result of cost savings achieved as a result of our increased focus on our key programs. These cost savings were primarily attributed to a decrease in personnel costs. In addition, under our Lilly collaboration extension, we are no longer reimbursing Lilly for the cost of their scientists who are supporting the joint collaboration.

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):

	December 31,	
	2006	2005
Alicaforsen for Crohn's disease	$ 5	$ 417
Other antisense development products	21,205	22,430
Development overhead costs	4,183	3,475
Non-cash compensation expense related to stock options	1,468	—
Total antisense drug development	$ 26,861	$ 26,322

Antisense drug development expenditures were $25.4 million, excluding $1.5 million of non-cash stock compensation expense, and $26.3 million for the years ended December 31, 2006 and 2005, respectively. The decrease of $929,000 for 2006 compared to 2005 was primarily due to a decrease in costs associated with development activities for our first generation drugs, including alicaforsen for Crohn's disease. In addition, we realized cost savings due to our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012, mipomersen, and ISIS 113715, and the resulting decision to discontinue development of ISIS 104838 and ISIS 14803.

We incurred development expenditures related to alicaforsen for Crohn's disease of $5,000 and $417,000 for the years ended December 31, 2006 and 2005, respectively. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with Crohn's disease. In these trials, alicaforsen did not demonstrate statistically significant induction of clinical remission

compared to placebo. As a result of this data, we decided not to invest further in the development of alicaforsen for Crohn's disease. The 2006 and 2005 expenses represent costs associated with closing out the program.

We incurred expenses related to our other products in development of $21.2 million and $22.4 million for the years ended December 31, 2006 and 2005, respectively. The decrease of $1.2 million in 2006 was primarily the result of a decrease in development activity related to alicaforsen for ulcerative colitis and the discontinuation of ISIS 104838 and ISIS 14803. In December 2004, we announced the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen enema produced significant and long-lasting disease improvement. Costs for alicaforsen for ulcerative colitis have decreased in 2006 as compared to 2005 because we were using primarily internal resources as we prepared Phase 3 development plans for the drug. The decreases were offset in part by increased expenditures related to our most promising second generation drugs, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the lowering of high cholesterol.

Development overhead costs were $4.2 million and $3.5 million for the years ended December 31, 2006 and 2005, respectively. The increase of $708,000 million for 2006 compared to 2005 was primarily due to increased personnel costs and costs associated with our amended license agreement with Ajinomoto.

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. These costs for the years ended December 31, 2006 and 2005 were $6.6 million and $6.5 million, respectively. 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.

Ibis Biosciences, Inc.

Ibis' research and development expenses are primarily the result of its performance under government contracts in support of the ongoing development of the Ibis T5000 Biosensor System and related assay kits. Ibis' expenses include all contract-related costs it incurs on behalf of government agencies in connection with the performance of its obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of the Ibis T5000 Biosensor System. Further, we allocate a portion of R&D support costs and selling, general and administrative costs to Ibis.

Ibis' research and development expenses, excluding $746,000 of non-cash compensation expense related to stock options for 2006, were $12.9 million for the years ended December 31, 2006 and 2005. In 2006, Ibis incurred costs to support deployed Ibis biosensor systems and the preparations necessary to move towards commercialization. These costs were offset by a decrease in pass-through equipment costs under our government contracts in 2006 compared to 2005.

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):

	December 31,	
	2006	2005
Personnel costs	$ 5,978	$ 5,739
Occupancy	5,868	6,931
Depreciation and amortization	6,955	5,696
Insurance	995	1,123
Other	1,720	2,055
Total R&D support costs	$ 21,516	$ 21,544

R&D support costs for the years ended December 31, 2006 and 2005 were both $21.5 million. In 2006, depreciation and amortization costs decreased compared to 2005 as a result of an increase in write-offs of patent application costs compared to 2005, offset in part by a decrease in facilities and equipment depreciation in 2006 compared to 2005. The decrease in facilities and equipment depreciation in 2006 compared to 2005 was the result of the consolidation and closure of facilities in 2005 resulting from our reorganization in 2005. In 2006 and 2005, we allocated $2.5 million and $2.8 million, respectively, of our R&D support costs to Ibis.

For the years ended December 31, 2006 and December 31, 2005, our R&D support costs by segment were as follows (in thousands):

	December 31,	
	2006	2005
Drug Discovery and Development	$ 18,998	$ 18,771
Ibis Biosciences	2,518	2,773
Total R&D support costs	$ 21,516	$ 21,544

Selling, General and Administrative Expenses

Selling, 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 Ibis sales and marketing. Additionally, we include in selling, 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. Beginning in 2006, as a result of the consolidation of Symphony GenIsis, selling, general and administrative expenses also include Symphony GenIsis' general and administrative expenses.

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

	December 31,	
	2006	2005
Selling, general and administrative expenses	$ 11,413	$ 8,432
Non-cash compensation expense related to stock options	1,206	—
Total selling, general and administrative as reported	$ 12,619	$ 8,432

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2006 totaled $11.4 million, compared to $8.4 million

for 2005. The increase for 2006 compared to 2005 was a result of increased selling, general and administrative expenses associated with the commercialization of the Ibis T5000 Biosensor System, the addition of general and administrative expenses that are consolidated from Symphony GenIsis and legal fees incurred for the Ajinomoto arbitration, which we settled in August 2006.

For the years ended December 31, 2006 and December 31, 2005, our selling, general and administrative expenses by segment were as follows (in thousands):

	December 31,	
	2006	2005
Drug Discovery and Development	$ 9,680	$ 7,342
Ibis Biosciences	2,939	1,090
Total selling, general and administrative expenses	$ 12,619	$ 8,432

Compensation Benefit Related to the Variable Accounting of Stock Options

Compensation benefit related to the variable accounting of stock options for the year ended December 31, 2005 was $544,000. Prior to the adoption of SFAS 123R, on January 1, 2006, we accounted for options affected by the employee stock option exchange program initiated in April 2003 as variable stock options in accordance with APB 25 and FIN 44.

Restructuring Activities

During the year ended December 31, 2006, we recorded a benefit of $536,000 compared to $7.0 million of expense in 2005 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.

The 2005 charge for restructuring activities consisted of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore.

Investment Income

Investment income for the years ended December 31, 2006 and 2005 was $6.0 million and $5.1 million, respectively. The increase in interest income in 2006 over 2005 was primarily due to our higher average returns on our investments resulting from higher interest rates for 2006 compared to 2005 and a higher average cash balance as a result of the funds held by Symphony GenIsis and the proceeds received from the Azimuth equity financing.

Interest Expense

Interest expense for the year ended December 31, 2006 was $9.0 million, compared to $20.3 million for the same period in 2005. The $11.3 million decrease from 2005 to 2006 was due to the effect of a lower debt balance during 2006 than during 2005, primarily related to the conversion of our $100 million Lilly loan in the third quarter of 2005.

Gain on Investments, net

Gain on investments for 2006 was $2.3 million and $0 for 2005. The gain on investments in 2006 reflected a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own, offset by a non-cash loss of $465,000 related to the impairment of our equity investment in ATL.

Net Loss Applicable to Common Stock

For the years ended December 31, 2006 and 2005, net loss applicable to common stock was $45.9 million and $72.4 million, respectively. We recognized a benefit of $23.0 million for 2006 in the Loss Attributable to Noncontrolling Interest in Symphony GenIsis, resulting from our collaboration with Symphony GenIsis. This benefit was a significant reason for the improvement in our net loss applicable to common stock in 2006 compared to 2005. The decrease in the net loss applicable to common stock was also impacted by a net gain on investments and a decrease in interest expense, offset in part by an increase in our loss from operations.

Net Loss per Share

Net loss per share for 2006 was $0.62 per share compared to $1.15 per share in 2005. During 2005, we issued 12 million shares of common stock in a private placement that raised net proceeds of approximately $48 million and 2.5 million shares to Lilly in connection with the conversion of our $100 million loan from Lilly. Additionally, in 2006, we issued approximately 8.0 million shares of common stock to Azimuth under an equity financing that raised proceeds of $75 million and we issued approximately 2.0 million shares in connection with the exercise of stock options and warrants. These additional shares, combined with the substantial decrease in net loss applicable to common stock, explain the significant decrease in our net loss per share for 2006 compared to 2005.

Net Operating Loss Carryforward

At December 31, 2006, we had federal, foreign and California tax net operating loss carryforwards of approximately $560.0 million, $1.0 million, and $179.5 million, respectively. We also had federal and California research credit carryforwards of approximately $25.7 million and $18.5 million, respectively. The net operating losses, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets. 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 will begin expiring in 2007, 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 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.

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, 2007, we have earned approximately $577.3 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, 2007, we have raised net proceeds of approximately $740.2 million from the sale of our equity securities and we have borrowed approximately $543.8 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2007, we had cash, cash equivalents and short-term investments of $193.7 million, which included $10.1 million of cash and cash equivalents held by Regulus, and stockholders' equity of $872,000. In comparison, we had cash, cash equivalents and short-term investments of $193.3 million and stockholders' equity of $68.6 million as of December 31, 2006. Even with the $80.4 million cash payment that we made in the third quarter of 2007 for the acquisition of Symphony GenIsis, our cash position at December 31, 2007 was virtually unchanged from the end of 2006, due to significant cash inflows including the:

- $30 million net cash received from the issuance of the $2^5/_8$% notes after repayment of the $5^1/_2$% notes,
- $15 million upfront licensing fee received from BMS,
- $26.5 million sublicensing fee received from Alnylam,
- $10 million invested in Regulus,
- $50 million upfront licensing fee and milestone payment received from OMI,
- $18 million of research and development funding from our partnerships, and
- $10.3 million from stock options exercised in 2007.

Not included in our cash balance at December 31, 2007 are the cash payments totaling $170 million that we received in early 2008 from our strategic partnerships with Genzyme and Abbott. In addition, upon the completion of the license agreement for mipomersen, Genzyme will pay us an additional $175 million. We also have the potential to receive up to $210 million from Abbott in exchange for the remainder of Ibis' stock.

At December 31, 2007, we had consolidated working capital of $145.1 million, compared to $181.1 million at December 31, 2006. In connection with our collaborations with BMS and OMI, we received large upfront payments, initially classified as liabilities, that we are amortizing into revenue over the collaboration terms, three and two years, respectively. A significant amount of the unamortized portion of these liabilities is included in current liabilities at December 31, 2007 and, as a result, our working capital at the end of 2007 is less than it was at the end of 2006.

As of December 31, 2007, our debt and other obligations totaled $170.1 million, compared to $140.3 million at December 31, 2006. The increase in our debt and other obligations was primarily due to the issuance of our $2^5/_8$% convertible subordinated notes, offset by the repayment of the $5^1/_2$% notes and the declining balance on our Silicon Valley Bank term loan. The significantly lower interest rate of the $2^5/_8$% convertible subordinated notes from that of our repaid $5^1/_2$% convertible subordinated notes reduces our cash interest payments by approximately $2.6 million per year. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Based on our existing cash and committed cash, including the $175 million mipomersen licensing fee from Genzyme, but not including the up to $210 million we could receive from Abbott, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years.

The following table summarizes our contractual obligations as of December 31, 2007. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided 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
Silicon Valley Bank Term Loan	$ 7.2	$ 7.2	$ —	$ —	$ —
Other Obligations	$ 0.4	$ —	$ —	$ —	$ 0.4
Operating Leases	$ 20.4	$ 2.9	$ 5.2	$ 3.4	$ 8.9

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a term loan from Silicon Valley Bank and other obligations.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire debt from two partners. We are amortizing the term loan over sixty months. The term loan requires monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 6.50% at December 31, 2007. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at December 31, 2007 was $7.2 million, which we expect to fully repay by December 31, 2008 according to the loan's terms.

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 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, we repaid the entire $125 million of our 5 1/2% convertible subordinated notes due 2009.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2007 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held 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 2007 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, 2007 to ensure that information required to be disclosed by us 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, 2007, 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, 2007.

The effectiveness of our internal control over financial reporting as of December 31, 2007 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, 2007, 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, 2007, 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, 2007 and 2006, and the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2007 of Isis Pharmaceuticals, Inc. and our report dated March 11, 2008, expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
March 11, 2008

Item 9B. Other Information

Not applicable

PART III

Item 10. Directors and Executive Officers of the Registrant

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 18, 2008 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2008 Annual Meeting of Stockholders to be held on June 4, 2008.

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, 2007.

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)	6,640,000	$	8.34	1,108,000(c)
Equity compensation plans not approved by stockholders(b)	1,544,000	$	9.18	2,195,000
Total	8,184,000	$	8.50	3,303,000

(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, 138,124 remained available for purchase under the ESPP as of December 31, 2007. 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, 2007, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 1,544,000 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 2,251,000 shares had been exercised under the 2000 Plan, and 2,195,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of 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 Consolidated Financial Statements, became fully vested on January 1, 2007 and will expire 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 shareholders 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. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. As of December 31, 2007, approximately 8,945 stock awards granted under the 2000 plan would have been accelerated in full if a transaction described above occurred at such date, even if the surviving corporation assumes such award. Beginning on May 16, 2007, new stock awards issued under the 2000 Plan will not be accelerated in full if a transaction desbribed above occurs.

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 82.

(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 14th day of March, 2008.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANELY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer (Principal executive officer)

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	March 14, 2008
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 14, 2008
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 14, 2008
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	March 14, 2008

/s/ JOSEPH KLEIN	Director	March 14, 2008
Joseph Klein, III.		
/s/ FREDERICK T. MUTO	Director	March 14, 2008
Frederick T. Muto		
/s/ JOHN C. REED, M.D. Ph.D.	Director	March 14, 2008
John C. Reed, M.D., Ph.D.		
/s/ JOSEPH H. WENDER	Director	March 14, 2008
Joseph H. Wender		

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)
4.3	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	Specimen Common Stock Certificate.(1)
4.5	Form of Right Certificate.(17)
4.7	Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(16)
4.8	Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 5 1/2% Convertible Subordinated Notes due 2009.(16)
4.9	Form of 5 1/2% Convertible Subordinated Note due 2009.(16)
4.10	Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(37)
4.11	Form of Warrant dated August 23, 2005.(37)
4.12	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.(42)
4.13	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein.(42)
4.14	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted).(3)
4.15	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)
10.4*	Registrant's Employee Stock Purchase Plan.(10)
10.5	Form of Employee Assignment of Patent Rights.(1)
10.6*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.11	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.13	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.14	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)

10.15	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.17	Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.18	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.19	Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.20	License Agreement between the Registrant and Atlantic Healthcare (UK) Limited dated March 7, 2007 (with certain confidential information deleted).(5)
10.21*	Retention Agreement dated September 21, 2007 between Isis and Mark K. Wedel. (8)
10.22	Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc. (with certain confidential information deleted).(22)
10.23	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.24	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)
10.26	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.35	Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(38)
10.36*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan.(43)
10.37*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(31)
10.41*	Form of Severance Agreement dated April 2003 entered into between the Registrant Stanley T. Crooke and B. Lynne Parshall.(32)
10.42	Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted). (33)
10.43*	Amendment No. 1 to Isis Pharmaceuticals, Inc. Employee Stock Purchase Plan.(33)
10.44	Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement.(12)
10.47	Subcontract No. 44076514 dated February 26, 2004 between the Registrant and Science Applications International Corporation (with certain confidential information deleted).(13)
10.48	Strategic Collaboration and License Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(18)
10.50	Amendment No. 1 to Sale Agreement dated October 14, 2007 between Isis and DRT 3.(15)

10.51	Development Agreement dated September 30, 2004 between the Registrant and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted).(34)
10.52	Amendment No. 1 to License Agreement between the Registrant and Eyetech.(39)
10.53	Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(39)
10.54	Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(39)
10.55*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(39)
10.56*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(39)
10.57*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(39)
10.58*	Offer Letter dated November 30, 2007 between the Company and Kleanthis Xanthopoulos.(23)
10.59	Amendment No.1 to Rights Agreement dated April 7, 2005.(35)
10.60	Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted).(36)
10.61	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(38)
10.62	Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(38)
10.63	Notice of Grant Award issued August 1, 2005 by the Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Disease (with certain confidential information deleted).(38)
10.64	Form of Subcontract Agreement between the Registrant and Science Applications International Corporation.(38)
10.65*	Letter dated February 27, 2006 extending Dr. Crooke's severance benefit agreement.(40)
10.66*	Letter dated February 27, 2006 extending Ms. Parshall's severance benefit agreement.(40)
10.67	Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(42)
10.68	Purchase Option Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).(3)
10.69	Collaboration and License Agreement between the Registrant and Bristol-Myers Squibb Company dated May 8, 2007 (with certain confidential information deleted). (7)
10.70	Amendment No. 1 to Manufacturing, Commercialization and Development Agreement Between the Registrant and Bruker Daltonics Inc. (with certain confidential information deleted). (7)

10.71*	Severance Agreement dated February 1, 2007 between the Registrant and Jeffrey M. Jonas.(44)
10.72	Manufacturing, Commercialization and Development Agreement between the Registrant and Bruker Daltonics, Inc. dated July 31, 2006 (with certain confidential information deleted).(45)
10.73	Research Agreement dated October 22, 2007 between the Registrant and CHDI, Inc. (with certain confidential information deleted).
10.74	Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007 (with certain confidential information deleted).(20)
10.75	License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).(20)
10.76	Limited Liability Company Agreement of Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).(20)
14.1	Registrant's Code of Ethics and Business Conduct.(12)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney.(46)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)

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

(2) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2004 Annual Meeting of Stockholders, filed with the SEC on April 12, 2004, 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 Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 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 Current Report on Form 8-K dated September 27, 2007 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 Annual Report Form 10-K for the year ended Dec 31, 2003 and incorporated herein by reference.

(13) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2004 and incorporated herein by reference.

(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, 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 Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated 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 Report on Form 8-K filed October 29, 2001 and incorporated herein by reference.

(22) Filed as an exhibit to the Registrant's Report on Form 8-K filed December 12, 2001 and incorporated herein by reference.

(23) Filed as an exhibit to the Registrant's Current Report on Form 8-K dated December 3, 2007 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, 2004 and incorporated herein by reference.

(27) Reserved.

(28) Reserved.

(29) Reserved.

(30) Reserved.

(31) 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.

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

(33) 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.

(34) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2004 and incorporated herein by reference.

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

(36) 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.

(37) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.

(38) 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.

(39) 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.

(40) Filed as an exhibit to Registrant's Current Report on Form 8-K dated February 27, 2006 and incorporated herein by reference.

(41) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2005 and incorporated herein by reference.

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

(43) 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.

(44) Filed as an exhibit to Registrant's Current Report on Form 8-K dated February 1, 2007 and incorporated herein by reference.

(45) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2006 and incorporated herein by reference.

(46) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2006, reference is made to page 82.

(47) Filed as an exhibit to the Registrants' Current Report on Form 8-K dated March 1, 2007 and incorporated herein by reference.

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

ISIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2007 and 2006, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2007. 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, 2007 and 2006, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2007, in conformity with U.S. generally accepted accounting principles.

As discussed in Note 1 to the consolidated financial statements, Isis Pharmaceuticals, Inc. changed its method of accounting for Share-Based Payments in accordance with Statement of Financial Accounting Standards No. 123 (revised 2004) on January 1, 2006.

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, 2007, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 11, 2008 expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
March 11, 2008

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

	December 31,	
	2007	2006
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Regulus Therapeutics LLC of $10.1 million at December 31, 2007 and $54.8 million held by Symphony GenIsis, Inc. at December 31, 2006)	$ 138,614	$ 114,514
Short-term investments	55,105	78,819
Contracts receivable	6,177	2,395
Inventories	2,817	861
Other current assets	4,604	9,614
Total current assets	207,317	206,203
Property, plant and equipment, net	7,131	7,157
Licenses, net	19,100	21,435
Patents, net	17,759	16,836
Debt issuance costs	4,740	1,400
Deposits and other assets	2,811	2,876
Total assets	$ 258,858	$ 255,907
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,507	$ 4,288
Accrued compensation	10,461	6,222
Accrued liabilities	6,794	6,071
Current portion of long-term obligations	7,238	7,514
Current portion of deferred contract revenue	33,205	1,044
Total current liabilities	62,205	25,139
5 1/2% convertible subordinated notes	—	125,000
2 5/8% convertible subordinated notes	162,500	—
Long-term obligations, less current portion	362	7,822
Long-term deferred contract revenue	23,548	44
Total liabilities	248,615	158,005
Noncontrolling interest in Symphony GenIsis, Inc.	—	29,339
Noncontrolling interest in Regulus Therapeutics LLC.	9,371	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 87,239,423 and 82,283,693 shares issued and outstanding at December 31, 2007 and 2006, respectively	87	82
Additional paid-in capital	827,992	880,954
Accumulated other comprehensive income	538	4,278
Accumulated deficit	(827,745)	(816,751)
Total stockholders' equity	872	68,563
Total liabilities, noncontrolling interest and stockholders' equity	$ 258,858	$ 255,907

See accompanying notes.

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

	Years Ended December 31,		
	2007	2006	2005
Revenue:			
Research and development revenue under collaborative agreements	$ 33,596	$ 15,091	$ 28,610
Licensing and royalty revenue	36,025	9,441	11,523
Total revenue	69,621	24,532	40,133
Expenses:			
Research and development	92,641	80,567	82,467
Selling, general and administrative	15,928	12,619	8,432
Compensation benefit related to variable accounting of stock options	—	—	(544)
Restructuring activities	—	(536)	6,960
Total operating expenses	108,569	92,650	97,315
Loss from operations	(38,948)	(68,118)	(57,182)
Other income (expense):			
Investment income	11,443	5,960	5,094
Interest expense	(7,573)	(9,029)	(20,313)
Gain on investments, net	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 LLC.	629	—	—
Net loss	(10,994)	(45,903)	(72,401)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc	(125,311)	—	—
Net loss applicable to common stock	$ (136,305)	$ (45,903)	$ (72,401)
Basic and diluted net loss per share	$ (1.63)	$ (0.62)	$ (1.15)
Shares used in computing basic and diluted net loss per share	83,739	74,308	62,877

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

Years Ended December 31, 2007, 2006 and 2005

(In thousands)

Description	Common stock Shares	Common stock Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2004	57,447	$ 57	$ 623,706	$ (72)	$ 2,623	$ (698,447)	$ (72,133)
Comprehensive Loss:							
Net loss applicable to common stock	—	—	—	—	—	(72,401)	(72,401)
Change in unrealized gains	—	—	—	—	555	—	555
Comprehensive loss	—	—	—	—	—	—	(71,846)
Deferred compensation	—	—	61	16	—	—	77
Options exercised and employee stock purchase plan	254	1	989	—	—	—	990
Compensation benefit relating to the granting of options	—	—	(678)	56	—	—	(622)
Conversion of Lilly debt	2,500	2	99,998	—	—	—	100,000
Private Placement Offering	12,000	12	46,187	—	—	—	46,199
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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Years Ended December 31,		
	2007	**2006**	**2005**
Operating activities:			
Net loss	$ (10,994)	$ (45,903)	$ (72,401)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	2,667	3,854	5,817
Amortization of patents	1,623	1,633	1,545
Amortization of licenses	2,335	2,335	2,326
Amortization of (discount)/premium on investments, net	(773)	(606)	697
Amortization of debt issuance costs	913	603	603
Share-based compensation expense	9,910	5,747	—
Compensation benefit related to variable accounting of stock options	—	—	(544)
Deferred interest on long-term debt	—	—	10,795
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	(23,157)	(23,021)	—
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC.	(629)	—	—
Gain on investments, net	(3,510)	(2,263)	—
Loss on early retirement of debt	3,212	—	—
Non-cash losses related to patents and property, plant and equipment	896	2,410	1,632
Income from variable accounting of stock warrants	—	—	(1,980)
Changes in operating assets and liabilities:			
Contracts receivable	(3,782)	1,523	5,380
Inventory	(1,956)	90	1,771
Other current and long-term assets	(494)	(796)	(610)
Accounts payable	(794)	1,214	(4,872)
Accrued compensation	4,239	2,516	231
Accrued liabilities	723	(2,135)	406
Deferred contract revenues	55,665	(426)	(11,840)
Net cash provided by (used in) operating activities	36,094	(53,225)	(61,044)
Investing activities:			
Purchase of short-term investments	(95,371)	(107,025)	(18,381)
Proceeds from the sale of short-term investments	119,956	72,575	51,029
Purchases of property, plant and equipment	(2,293)	(1,042)	(422)
Proceeds from the sale of property, plant and equipment	—	—	14,020
Acquisition of licenses and other assets	(2,717)	(1,514)	(2,451)
Proceeds from the sale of strategic investments	5,181	4,397	3,283
Acquisition of Symphony GenIsis, Inc.	(80,400)	—	—
Net cash provided by (used in) investing activities	(55,644)	(32,609)	47,078
Financing activities:			
Net proceeds from issuance of equity	11,351	86,364	49,168
Proceeds from issuance of $2^{5}/_{8}$% convertible subordinated notes, net of issuance costs	157,056	—	—
Proceeds from long-term borrowing	—	—	4,603
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	(7,736)	(7,851)	(16,170)
Proceeds from capital contribution to Regulus Therapeutics LLC	10,000	—	—

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS (Continued)

(In thousands)

Proceeds from contribution to noncontrolling interest in Symphony GenIsis, Inc., net of fees	—	70,950	—
Net cash provided by financing activities	43,650	149,463	37,601
Net increase in cash and cash equivalents	24,100	63,629	23,635
Cash and cash equivalents at beginning of year	114,514	50,885	27,250
Cash and cash equivalents (including cash and cash equivalents held by Regulus Therapeutics LLC of $10.1 million at December 31, 2007 and $54.8 million held by Symphony GenIsis, Inc. at December 31, 2006) at end of year	$ 138,614	$ 114,514	$ 50,885
Supplemental disclosures of cash flow information:			
Interest paid	$ 6,212	$ 8,431	$ 8,877
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ —	$ 18,590	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Common stock issued for Symphony GenIsis, Inc. acquisition	$ 51,093	$ —	$ —
Amounts accrued for capital and patent expenditures	$ 1,013	$ 979	$ 397
Acquisition of property, plant and equipment	$ —	$ 361	$ —
Conversion of receivables into long-term investment	$ —	$ —	$ 750
Conversion of debt into common stock	$ —	$ —	$ 100,000

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, Ibis Biosciences, Inc., Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Ltd., Orasense, Ltd. and Symphony GenIsis, Inc. On January 30, 2008, Ibis became a majority-owned subsidiary of ours due to Abbott Molecular Inc.'s investment in Ibis as more fully described in *Note 6—Collaborative Arrangements and Licensing Agreements*. On September 27, 2007, we purchased all of the equity in Symphony GenIsis as more fully described in *Note 6—Collaborative Arrangements and Licensing Agreements*. On October 25, 2006, we dissolved the Orasense, Ltd. subsidiary. As more fully described in *Note 8—Restructuring Activities,* we closed our Singapore operations in early 2005. In addition to our wholly owned subsidiaries, the consolidated financial statements at December 31, 2007 include one variable interest entity, Regulus Therapeutics LLC, 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*. 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 also include the financial condition and results of operations of Symphony GenIsis. All significant intercompany balances and transactions have been eliminated.

Organization and business activity

We were incorporated in California on January 10, 1989. In conjunction with our initial public offering, we were 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 Statement of Financial Accounting Standards ("SFAS") 128, *Earnings per Share*. We compute basic loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period ("Basic EPS method"). We compute diluted loss per common share using the weighted-average number of common and dilutive common equivalent shares outstanding during the period ("Diluted EPS method"). Diluted common equivalent shares of 18.6 million at December 31, 2007 consisted of shares issuable upon exercise of stock options, warrants and convertible debt. As we incurred a loss in the years ended December 31, 2007, 2006 and 2005, 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 earned 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 or 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, 2007, 2006 and 2005, research and development costs of approximately $17.6 million, $13.6 million, and $30.4 million, respectively, were related to collaborative research and development arrangements.

1. Organization and Significant Accounting Policies (Continued)

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 billed our customers or received payment from our customers in advance of recognizing revenue, the amounts are included 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. Should different estimates prevail, revenue recognized could be materially different. To date our estimates have not required material adjustments. 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 activities to be performed 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 date 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, as defined by 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 are not obligated for future performance 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 the provisions in SAB 104 were met 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.

In the fourth quarter of 2006, we started to sell the Ibis T5000 Biosensor System commercially. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since we had no previous

1. Organization and Significant Accounting Policies (Continued)

experience commercially selling the Ibis T5000 Biosensor System, we had no basis to determine the fair values of the various elements included in each system; therefore, we account for the entire system as one deliverable and recognize revenue over the period of performance. The assay kits, which are sold separately from the instrument, are considered part of the system from an accounting perspective because the assay kits and the instrument are dependent on each other. For a one-year period following the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System; therefore, we are amortizing the revenue for the entire system, including related assay kits, over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

As part of our Eli Lilly and Company alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the companies' research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, we converted the loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration.

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, U.S. government agencies and U.S. municipalities. 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 marketable securities at fair market value based upon market prices quoted 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.

In addition to investments in marketable securities, we have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the

1. Organization and Significant Accounting Policies (Continued)

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. Unrealized gains and losses related to temporary declines are recorded as a separate component of stockholders' equity. 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 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 on investment of $465,000 related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Ltd. Since the impairment in the second quarter of 2006, we have recorded a net unrealized gain of $531,000 related to our equity investment in ATL as a separate component of stockholders' equity, reflecting the increase in the market value of the investment since the impairment. We determined that there were no other-than-temporary declines in value of investments in 2007 and 2005.

Inventory valuation

In accordance with Statement of Financial Accounting Standards ("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. Each of our raw materials can be used in multiple products and, as a result, has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug could be used 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. Also included in inventory are material costs and related manufacturing costs associated with the Ibis T5000 Biosensor System and related assay kits. 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 considered 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, 2007, 2006 and 2005.

Total inventory includes the following as of December 31, 2007 and 2006 (in thousands):

	December 31,	
	2007	2006
Raw materials	$ 2,679	$ 861
Work-in-process	138	—
	$ 2,817	$ 861

1. Organization and Significant Accounting Policies (Continued)

Property, plant and equipment

Property, plant and equipment are stated at cost and consist of the following (in thousands):

	December 31,	
	2007	2006
Equipment and computer software	$ 25,035	$ 22,761
Leasehold improvements	12,081	11,758
Furniture and fixtures	1,542	1,533
	38,658	36,052
Less accumulated depreciation	(31,527)	(28,895)
	$ 7,131	$ 7,157

Depreciation of property, plant and equipment is provided on the straight-line method over estimated useful lives as follows:

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

Leasehold improvements are depreciated 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, 2007 and 2006. 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. Accumulated amortization related to licenses was $16.8 million and $14.5 million at December 31, 2007 and 2006, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2008, 2009, 2010 and 2011 and $2.2 million for the year ending December 31, 2012.

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 determine 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 patents are issued. The weighted average remaining life of issued patents was 4.1 years and 4.6 years at December 31, 2007 and 2006, respectively. In 2007, 2006 and 2005, we recorded a non-cash charge of $896,000, $2.8 million and $1.7 million, respectively, which primarily is included in research and development expenses and is related to the write-down of our patent costs to their estimated net realizable values.

1. Organization and Significant Accounting Policies (Continued)

Accumulated amortization related to patents was $10.2 million and $8.6 million at December 31, 2007 and 2006, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)
2008	$ 1.6
2009	$ 1.5
2010	$ 1.3
2011	$ 1.1
2012	$ 0.9

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, *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. We recorded a charge of $896,000, $2.4 million and $15.6 million for the years ended December 31, 2007, 2006 and 2005, respectively, primarily related to 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, 2007, we had collaborative arrangements with nine entities that we consider to be variable interest entities ("VIE") under FIN 46R. Described below is our relationship with Symphony GenIsis and the collaborative arrangements entered into in 2007 that we consider to be VIE's.

1. Organization and Significant Accounting Policies (Continued)

In April 2006, we entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to fund the development of our cholesterol-lowering drug, mipomersen (formerly ISIS 301012), and two novel drugs from our metabolic disease program, ISIS 325568 and ISIS 377131. Symphony Capital formed Symphony GenIsis, capitalized with $75.0 million, to provide funding for the development of these three drugs in collaboration with us. We treated Symphony GenIsis as a VIE for which we were the primary beneficiary. As a result, beginning in the second quarter of 2006, we included the financial condition and results of operations of Symphony GenIsis in our consolidated financial statements. The creditors of Symphony GenIsis did not have recourse to our general credit. In September 2007, we purchased all of the equity of Symphony GenIsis at which point it became our wholly owned subsidiary and ceased being a VIE. (See *Note 6—Collaborative Arrangements and Licensing Agreements).*

Had we acquired Symphony GenIsis at its inception, we would have reported the following pro forma amounts for net loss applicable to common stock and basic and diluted net loss per share (in thousands, except per share amounts) for the years ended December 31, 2007 and 2006:

	Year Ended December 31,	
	2007	2006
Net loss applicable to common stock—as reported	$ (136,305)	$ (45,903)
Net loss applicable to common stock—pro forma	$ (162,598)	$ (72,261)
Basic and diluted net loss per share—as reported	$ (1.63)	$ (0.62)
Basic and diluted net loss per share—pro forma	$ (1.87)	$ (0.94)

On a proforma basis, there are no changes to our reported revenue in 2007 and 2006. Additionally, since Symphony GenIsis was formed in 2006, on a pro forma basis, there is no change to our 2005 results of operations.

As part of the collaboration between Atlantic Healthcare (UK) Limited and us, during March 2007, we licensed alicaforsen, our ICAM-1 antisense drug, to Atlantic, in exchange for $2.0 million of Atlantic's common stock. We have recognized a valuation allowance of $2.0 million to offset the equity instrument, as realization of this asset is uncertain. We are not required to consolidate Atlantic's results of operations under FIN 46R as we are not the primary beneficiary.

In September 2007, we and Alnylam formed Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Alnylam made an initial investment of $10.0 million to balance venture ownership; thereafter we and Alnylam will share funding of Regulus. Regulus is operating as an independent company with a separate Board of Directors 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 treat Regulus as a VIE for which we are the primary beneficiary. As a result, beginning in the third quarter of 2007, we included the financial condition and results of operations of Regulus in our consolidated financial statements. The creditors of Regulus do not have recourse to our general credit.

In October 2007, we granted an exclusive worldwide license to Altair Therapeutics Inc. for the development and commercialization of ISIS 369645, an inhaled inhibitor of the IL-4/IL-13 signaling pathways for the treatment of asthma in exchange for 18 percent of Altair's Series A preferred stock.

1. Organization and Significant Accounting Policies (Continued)

We have recognized a full valuation allowance to offset the equity instrument, as realization of this asset is uncertain. We are not required to consolidate Altair's results of operations under FIN 46R as we are not the primary beneficiary.

In November 2007, we granted Excaliard Pharmaceuticals, Inc. an exclusive worldwide license for the development and commercialization of certain antisense drugs in exchange for a $1.0 million cash payment and $1.0 million of Excaliard's Series A preferred stock. We have recognized a valuation allowance of $1.0 million to offset the equity instrument, as realization of this asset is uncertain. We are not required to consolidate Excaliard's results of operations under FIN 46R as we are not the primary beneficiary.

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. SFAS 123R supersedes our previous accounting under Accounting Principles Board Opinion ("APB") 25, *Accounting for Stock Issued to Employees* and SFAS 123, *Accounting for Stock-Based Compensation*, beginning January 1, 2006. 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.

We adopted SFAS 123R using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of fiscal year 2006. Our Consolidated Statements of Operations for the years ended December 31, 2007 and 2006 reflect the impact of SFAS 123R. In accordance with the modified prospective transition method, our Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact 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. The value of the portion of the award that is ultimately expected to vest is recognized as expense over the requisite service period as stock-based compensation expense in our Consolidated Statements of Operations. For the years ended December 31, 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. As stock-based compensation expense recognized in the Statements of Operations for the years ended December 31, 2007 and 2006 are based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123R requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual

1. Organization and Significant Accounting Policies (Continued)

forfeitures differ from those estimates. In our pro forma information required under SFAS 123 for the periods prior to fiscal 2006, we accounted for forfeitures as they occurred.

As permitted by SFAS 123R, we utilize the Black-Scholes option-pricing model ("Black-Scholes model") as our method of valuation for stock-based awards granted. The Black-Scholes model was previously utilized for our pro forma information required under SFAS 123. Our determination of the estimated fair value of stock-based payment awards on the date of grant using an option-pricing model is affected by our stock price as well as assumptions regarding a number of highly complex and subjective variables. 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 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.

Prior to January 1, 2006, we had adopted the disclosure-only provision of SFAS 123. Accordingly, we had not previously recognized compensation expense for our stock option plans and employee stock purchase plan, except for compensation expense primarily related to the affected options from the 2003 option exchange program. Non-cash stock-based compensation expense recognized under SFAS 123R for the years ended December 31, 2007 and 2006 was $9.9 million and $5.7 million, respectively. The non-cash stock-based compensation benefit resulting from the 2003 option exchange program for the years ended December 31, 2005 was $544,000.

In April 2003, we implemented an employee stock option exchange program ("2003 option exchange program"). The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1 million options having an exercise price of $5.15. The new options were fully vested as of January 31, 2006, and expire on December 31, 2008. Prior to January 1, 2006, we accounted for the affected options using variable accounting consistent with the provisions of APB 25 and FIN 44, *Accounting for Certain Transactions involving Stock Compensation—an interpretation of APB Opinion 25.* As a result, we recorded non-cash compensation expense/benefit related to stock options on our Consolidated Statements of Operations.

See *Note 4—Stockholders' Equity* for additional information regarding our share-based compensation plans and the impact of adopting SFAS 123R.

1. Organization and Significant Accounting Policies (Continued)

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, 2007, 2006 and 2005 has been reflected in our Consolidated Statements of Stockholders' Equity.

Segment information

We operate in two separate segments; Drug Discovery and Development and our Ibis subsidiary. In accordance with SFAS 131, *Disclosure about Segments of an Enterprise and Related Information*, we provide segment financial information and results for Drug Discovery and Development and Ibis based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment. We do not include asset or liability information by reportable segment since it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

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. Under FIN 48, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. 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 September 2006, the FASB issued SFAS 157, *Fair Value Measurements.* This Statement defines fair value, establishes a framework for measuring fair value in generally accepted accounting principles and expands disclosures about fair value measurements. This Statement applies across a broad number of other accounting pronouncements that require or permit fair value measurements. This Statement is effective for all financial statements issued for fiscal years that begin after November 15, 2007. We are currently evaluating the impact of adopting SFAS 157 to determine the effects, if any, on our operating results and financial position.

1. Organization and Significant Accounting Policies (Continued)

In February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities*, which allows entities to account for most financial instruments at fair value rather than under other applicable generally accepted accounting principles ("GAAP"), such as historical cost. Under SFAS 159, a financial instrument is marked to fair value every reporting period with the gain/loss from a change in fair value recorded in the statement of operations. SFAS 159 is effective for all financial statements issued for fiscal years that begin after November 15, 2007. We do not expect this new guidance to have a material impact on our financial statements.

In June 2007, the FASB ratified EITF No. 07-3, *Accounting for Nonrefundable Advance Payments for Goods or Services Received for Use in Future Research and Development Activities*. EITF No. 07-3 requires that nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities pursuant to executory contractual arrangements be deferred and recognized as an expense in the period that the related goods are delivered or services are performed. EITF No. 07-3 is effective for fiscal years beginning after December 15, 2007 and, as such, we plan to adopt the provisions of EITF No. 07-3 as of January 1, 2008. We do not expect this new guidance to have a material impact on our financial statements.

In December 2007, the FASB issued SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, and amendment to ARB No. 51*. This statement states that accounting and reporting for minority interests will be recharacterized as noncontrolling interests and classified 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. We are currently evaluating the impact of adopting SFAS 160 on our results of operations and financial position.

2. Investments

As of December 31, 2007, our excess cash is primarily invested in commercial paper and debt instruments of financial institutions, corporations, U.S. government agencies and U.S. municipalities with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to maximize trends in yields and interest rates without compromising safety and liquidity. All of the available-for-sale securities held by us at December 31, 2007 have a contract maturity of 1 year or less.

We have an ownership interest of less than 20% in each of six private companies and two public companies we conduct business with, and account for them under the cost method of accounting according to APB 18. The companies are ATL and iCo Therapeutics Inc., which are publicly-traded, and Santaris Pharma A/S (formerly Pantheco A/S), OncoGenex Technologies Inc., Achaogen, Inc., Atlantic Healthcare, Altair and Excaliard, which are privately-held. In determining if and when a decrease in market value below cost in our equity positions is other-than-temporary, we examine historical trends in stock price, the financial condition and near term prospects of the issuer, and our current need for cash. 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. See *Note 1—Organization and Significant Accounting Policies* for a discussion of impairment losses incurred in 2007, 2006 and 2005.

2. Investments (Continued)

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

December 31, 2007	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
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

December 31, 2006	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
U.S. corporate debt securities	$ 71,361	$ 3	$ (9)	$ 71,355
Debt securities issued by U.S. government agencies	2,998	—	(31)	2,967
Total short-term investments	74,359	3	(40)	74,322
Debt securities issued by U.S. government agencies	4,526	—	(29)	4,497
Total long-term investments	4,526	—	(29)	4,497
Subtotal	$ 78,885	$ 3	$ (69)	$ 78,819
Equity securities:				
Short-term portion	2,561	4,344	—	6,905
Long-term portion	2,125	—	—	2,125
Subtotal	$ 4,686	$ 4,344	$ —	$ 9,030
	$ 83,571	$ 4,347	$ (69)	$ 87,849

2. Investments (Continued)

Investments considered to be temporarily impaired at December 31, 2007 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Fair Value	Unrealized Losses
Available-for-sale securities:			
U.S. corporate debt securities	6	$ 12,410	$ (4)
Total temporarily impaired securities	6	$ 12,410	$ (4)

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.

3. Long-Term Obligations and Commitments

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

	December 31,	
	2007	2006
Standard operating debt	$ 7,238	$ 13,951
5 1/2% convertible subordinated notes	—	125,000
2 5/8% convertible subordinated notes	162,500	—
Other obligations	362	1,385
Total	$ 170,100	$ 140,336
Less: current portion	(7,238)	(7,514)
Total Long-Term Obligations	$ 162,862	$ 132,822

Standard Operating Debt

In December 2003, we obtained a $32.0 million term loan from Silicon Valley Bank. The term loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The term loan bears interest at the prime rate less applicable discounts (6.50% at December 31, 2007), is payable in monthly payments of principal and interest, matures in December 2008, and is convertible at our election to a fixed rate at the then-applicable prime rate plus 1.25%. The term loan is subject to certain liquidity and other covenants, including a requirement that we maintain a minimum balance in an account at the lending bank at all times equal to the outstanding balance of the loan. We were in compliance with these covenants as of December 31, 2007 and 2006. The carrying value of this loan at December 31, 2007 and 2006 was $7.2 million and $14.0 million, respectively, which approximated fair value.

3. Long-Term Obligations and Commitments (Continued)

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 include 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, 2007, the principal and accrued interest outstanding on the notes was $162.5 million and $1.6 million, respectively, and the fair value was $208.3 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 interest 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.

Capital Leases and Other Obligations

At December 31, 2006, we had $1.0 million outstanding under various capital equipment leases, which bore interest at rates ranging from 7.25% to 8.78% and were set to mature in January 2008. In December 2007, we paid off the remaining capital lease obligation; therefore, there are no capital leases outstanding at December 31, 2007. As of December 31, 2007 and 2006, we had approximately $362,000 and $378,000, respectively, under various contractual obligations.

Annual debt and other obligation maturities at December 31, 2007 are as follows (in thousands):

2008	$ 7,238
2009	1
2010	1
2011	1
2012	1
Thereafter	162,858
Total	$ 170,100

We lease certain office equipment and office and lab space under non-cancelable operating leases with terms through September 2020. The lease for the building that houses Ibis expires in 2010 and has two five-year options to extend the lease. The lease on the building we primarily use for laboratory and

3. Long-Term Obligations and Commitments (Continued)

office space for our drug development business expires in 2012 and has a 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 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. We recently entered into a lease for additional office and lab space for our drug development business. The lease for this space expires in 2011 and has two five-year options to extend the lease.

Annual future minimum payments under operating leases as of December 31, 2007 are as follows (in thousands):

	Operating Leases
2008	$ 2,896
2009	2,868
2010	2,367
2011	1,939
2012	1,464
Thereafter	8,859
Total minimum payments	$ 20,393

Rent expense for the years ended December 31, 2007, 2006, and 2005 was $3.4 million, $3.2 million, and $2.6 million, respectively. Cost of equipment under outstanding capital leases and the related accumulated depreciation at December 31, 2006 was approximately $3.2 million and $2.5 million, respectively. There were no outstanding capital leases at December 31, 2007.

4. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2007 and 2006, 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 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share

4. Stockholders' Equity (Continued)

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.

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, 2007 and 2006, we had 200,000,000 shares of common stock authorized, of which 87,239,423 and 82,283,693 were issued and outstanding, respectively. As of December 31, 2007, total common shares reserved for future issuance were approximately 25,918,498.

During 2007 and 2006, we issued 1.5 million and 1.9 million shares of common stock, respectively, for stock option exercises and ESPP purchases. The net proceeds received from these transactions were $11.4 million and $11.5 million in 2007 and 2006, respectively.

In January 2008, Genzyme Corporation purchased 5.0 million shares of our common stock for $150.0 million as part of the strategic alliance to develop and commercialize mipomersen.

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.

In May 2006, we entered into a Common Stock Purchase Agreement with Azimuth Opportunity Ltd. During 2006, Azimuth purchased approximately 8.0 million shares of our common stock for $75.0 million at a weighted average price of $9.41 per share. Deducting transaction fees, we received net proceeds of $74.9 million.

Stock Option Plans

1989 Stock Option Plan

In June 1989 and as amended, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to our employees, directors, and consultants. The term of the plan is scheduled to end 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 before January 1, 1996 generally vested over a five-year period. 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, 2007, a total of 6,201,808 options were outstanding, options to purchase 2,717,282 shares were exercisable, and 666,653 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 provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of

4. Stockholders' Equity (Continued)

common stock to our employees, directors, and consultants. In May 2002, our Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 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 became fully vested on January 1, 2007 and will expire on December 31, 2008. At December 31, 2007, a total of 1,543,878 options were outstanding, 1,488,933 shares were exercisable, and 2,195,309 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. With respect to any other stock awards outstanding under the 2000 Plan and the 1989 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. As of December 31, 2007, options to purchase approximately 8,945 shares granted under the 2000 Plan would have been accelerated in full if a transaction described above occurred at such date, even if the surviving corporation assumes such award. Beginning on May 16, 2007, new stock awards issued under the 2000 Plan will not be accelerated in full if a transaction desbribed above occurs.

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 new 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

4. Stockholders' Equity (Continued)

December 31, 2007, a total of 438,000 options were outstanding, 256,750 of the shares issued under this plan were exercisable and 303,000 shares were available for future grant.

Employee Stock Purchase Plan

In 2000, our Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan ("ESPP") and we reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the ESPP, resulting in a total of 1.6 million shares authorized in the plan as of December 31, 2007. The plan 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 2007, 161,930 shares were purchased and issued under this plan to employees at prices ranging from $5.14 to $8.23 per share. At December 31, 2007, 138,124 shares were available for purchase under this plan.

Stock Option Activity and Stock-Based Compensation Expense

The following table summarizes stock option activity for the year ended December 31, 2007 (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, 2006	7,656	$ 7.57		
Granted	2,378	$ 11.26		
Exercised	(1,378)	$ 7.50		
Cancelled/forfeited/ expired	(472)	$ 10.21		
Outstanding at December 31, 2007	8,184	$ 8.50	4.76	$ 60,350
Exercisable at December 31, 2007	4,463	$ 7.93	3.87	$ 35,714

4. Stockholders' Equity (Continued)

The following table summarizes information concerning outstanding and exercisable options as of December 31, 2007 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$2.96–$5.25	1,575	4.80	$ 5.08	807	$ 5.03
$5.35–$6.81	1,973	4.59	$ 6.27	1,546	$ 6.38
$6.81–$9.50	1,392	4.13	$ 7.53	1,077	$ 7.39
$9.63–$11.02	838	4.64	$ 10.08	456	$ 9.93
$11.12–$11.12	1,570	5.98	$ 11.12	0	$ 0.00
$11.13–$22.83	836	3.92	$ 15.31	577	$ 15.60
	8,184	4.76	$ 8.50	4,463	$ 7.93

The weighted-average estimated fair values of options granted were $6.19, $3.44 and $3.62 for the years ended December 31, 2007, 2006 and 2005, respectively. The total intrinsic value of options exercised during the years ended December 31, 2007, 2006 and 2005 were $9.5 million, $6.6 million and $20,000, respectively, which was determined as of the date of exercise. The amounts of cash received from the exercise of stock options were $10.3 million, $10.9 million and $147,000 for the years ended December 31, 2007, 2006 and 2005, respectively. For the year ended December 31, 2007, the weighted-average fair value of options exercised was $14.39. As of December 31, 2007, there was $9.8 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted 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 stock options and employee stock purchases under SFAS 123R for the year ended December 31, 2007 (in thousands, except per share data), which was allocated as follows:

	Year Ended December 31,	
	2007	2006
Research and development	$ 7,920	$ 4,541
Selling, general and administrative	1,990	1,206
Non-cash compensation expense related to stock options included in operating expenses	$ 9,910	$ 5,747
Basic and diluted net loss per share	$ 0.12	$ 0.08

4. Stockholders' Equity (Continued)

As part of the Regulus joint venture, both Alnylam and we issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. These options are recorded on Regulus' books. Since we are consolidating the financial results of Regulus, the non-cash stock based compensation expense associated with these options of $412,000 is included in our consolidated expenses.

Prior to the adoption of SFAS 123R, we had adopted the disclosure-only provision of SFAS 123. Accordingly, we had not previously recognized compensation expense for the stock option plans and the ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program. In addition, we presented deferred compensation as a separate component of stockholders' equity. In accordance with the provisions of SFAS 123R, on January 1, 2006, we reclassified the balance in deferred compensation to additional paid-in capital on the balance sheet.

Had we recorded compensation expense consistent with SFAS 123, we would have reported the following pro forma amounts for net loss applicable to common stock and basic and diluted net loss per share (in thousands, except per share amounts) for the year ended December 31, 2005:

	Year Ended December 31, 2005
Net loss applicable to common stock—as reported	$ (72,401)
Net loss applicable to common stock—pro forma	$ (76,660)
Basic and diluted net loss per share—as reported	$ (1.15)
Basic and diluted net loss per share—pro forma	$ (1.22)

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.

4. Stockholders' Equity (Continued)

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, 2007, 2006 and 2005:

Employee Stock Option Grants:

	December 31,		
	2007	2006	2005
Risk-free interest rate	4.6%	4.9%	4.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	63.1%	68.6%	81.7%
Expected Life	4.6 years	4.6 years	4.8 years

Board of Director Stock Option Grants:

	December 31,		
	2007	2006	2005
Risk-free interest rate	4.9%	5.1%	4.2%
Dividend yield	0.0%	0.0%	0.0%
Volatility	65.5%	85.2%	70.7%
Expected Life	7.4 years	7.0 years	4.8 years

ESPP:

	December 31,		
	2007	2006	2005
Risk-free interest rate	5.1%	4.8%	3.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	51.1%	49.9%	53.4%
Expected Life	6 months	6 months	6 months

Risk-Free Interest Rate. The risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. The dividend yield assumption is based 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. Prior to fiscal 2006, we also used our historical stock price volatility in accordance with SFAS 123 for purposes of our pro forma information. 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 they are expected to be outstanding. For the 2002 Plan, we estimated the expected term of options granted based on historical exercise patterns. For the other two stock option plans, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107.

4. Stockholders' Equity (Continued)

Forfeitures. As stock-based compensation expense recognized in the Consolidated Statements of Operations is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123R requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Forfeitures were estimated based on historical experience. Our historical forfeiture estimates have not been materially different from our actual forfeitures. In our pro forma information required under SFAS 123 for the period prior to fiscal 2006, we accounted for forfeitures as they occurred.

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. The warrants issued in the private placement provide a call right in our favor to the extent that the price per share of our common stock exceeds $14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. We cannot exercise this call right prior to August 2008. As of December 31, 2007, 2.5 million shares of common stock under the warrants remained outstanding.

Prior to the registration statement for the August private placement financing becoming effective, the potential existed for us to pay liquidated damages if such effectiveness did not occur. Accordingly, as required by EITF 00-19, *"Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,"* we periodically revalued these warrants as a derivative instrument by computing the value in connection with changes in the underlying stock price and other assumptions, with the change in value recorded as interest expense or interest income. Before November 1, 2005, the effective date of the underlying registration statement, the warrant liability was recorded at fair value, which was determined using the Black-Scholes option-pricing model. Changes in fair value during each period were recorded as interest income. On November 1, 2005, the effective date of the underlying registration statement, the warrant liability was reclassified into stockholders' equity.

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, 2007, 4.2 million 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

4. Stockholders' Equity (Continued)

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.

5. 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. Under FIN 48, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. 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 $204.1 million and research and development credits of $38.1 million generated from our inception until December 31, 2007. Due to uncertainties surrounding our ability to generate future taxable income to realize these assets, a full valuation has been established 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

5. Income Taxes (Continued)

analysis. However, we plan to complete a Section 382 analysis in 2008 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 percent valuation allowance, future changes in our unrecognized tax benefits will not impact our effective tax rate or our financial statements.

We are subject to taxation in the U.S. 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, 2007, we did not recognize any interest or penalties.

Our deferred tax liabilities were $6.3 million and $5.7 million at December 31, 2007 and 2006, 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, 2007 until we complete a Section 382 analysis. Our remaining deferred tax assets at December 31, 2007 were $50.8 million and our deferred tax assets at December 31, 2006 were $294.2 million, including the net operating losses and research and development credits. A full valuation allowance of $44.5 million and $288.4 million has been established to offset the net deferred tax assets as of December 31, 2007 and 2006, respectively, as realization of these assets is uncertain.

As a result of the adoption of SFAS 123R, we recognize excess tax benefits associated with the exercise of stock options directly to stockholders' equity only when realized. Accordingly, deferred tax assets are not recognized for net operating loss carryforwards resulting from excess tax benefits occurring from January 1, 2006 onward. At December 31, 2007 deferred tax assets do not include excess tax benefits from stock-based compensation of approximately $15.6 million.

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 and development tax credit carryforwards of approximately $25.9 million and $19.2 million, respectively. 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. Unless previously utilized, the expiration of tax loss carryforwards began in 2007. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership.

6. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Genzyme Corporation

In January 2008, we announced a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. Mipomersen is our lipid-lowering drug targeting apoB-100. As part of the strategic relationship, Genzyme has exclusively licensed mipomersen and will also have preferred access to our future drugs for CNS and certain rare diseases. Genzyme paid us $150 million to purchase five million shares of our common stock for $30 per share and upon the completion of the license agreement Genzyme will also pay us a $175 million upfront license fee for mipomersen. In addition to this initial $325 million, we also have the potential to receive up to $825 million in development and regulatory milestone payments and up to $750 million in commercial milestone payments. Under the agreement, we will also share profits with Genzyme, with our share being 50% for annual revenues of $2 billion or greater, and increasing linearly from 30% to 50% as annual revenues ramp up to $2 billion. We have committed to spend $75 million of development costs over the next few years. Genzyme will take over full development and commercialization responsibilities thereafter.

Genzyme has agreed that it will not sell its Isis stock until the earlier of 4 years from the date of our mipomersen license agreement, the first commercial sale of mipomersen and the termination of the our mipomersen license 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 agreement and 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.

Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with OMI to discover, develop and commercialize antisense drugs to treat metabolic diseases, including type 2 diabetes. As part of the collaboration, we granted OMI worldwide development and commercialization rights to two of our diabetes drugs, ISIS 325568 and ISIS 377131, which selectively inhibit the production of GCGR and GCCR, respectively. Additionally, OMI is providing funding to us to support a focused research program in metabolic disease. Under the terms of the agreement, OMI 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. OMI 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 milestones 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 of ISIS 325568 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 2007, we recognized revenue of $13.2 million related to the upfront licensing fee, the milestone payment and the initial research and development funding, which represented 19% of our

6. Collaborative Arrangements and Licensing Agreements (Continued)

total revenue for 2007. Our balance sheet at December 31, 2007 includes deferred revenue of $41.7 million related to the upfront licensing fee and milestone payment.

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 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 a period of three years. We will also receive up to $168 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 2007, we recognized revenue of $5.2 million related to the upfront licensing fee and the research funding, which represented 8% of our total revenue for 2007. Our balance sheet at December 31, 2007 includes deferred revenue of $11.7 million related to the upfront licensing fee and the research funding.

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, 2007, we earned milestone payments totaling $1.2 million under the collaboration agreement. Pfizer will also pay us additional milestone payments under the collaboration agreement if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, we will earn milestone payments totaling up to $26.1 million. In addition, under the collaboration agreement, we will receive royalties on the sale of drugs resulting from the collaboration. During 2007, 2006 and 2005, we earned revenue of $445,000, $547,000 and $2.2 million, respectively. Our balance sheets as of December 31, 2007 and December 31, 2006 included deferred revenue of $900,000 and $420,000, respectively, related to our agreements 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 and a $100 million loan that Lilly provided to us to fund our obligations under the research collaboration. In August 2005, we extended the research collaboration with Lilly to focus on a select number of targets. During the extension, we and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue our efforts to develop and refine antisense technologies. During the extension, we are using collaboration funds to support our scientists and Lilly is supporting Lilly scientists. The extended collaboration provides Lilly access to our patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the

6. Collaborative Arrangements and Licensing Agreements (Continued)

extension, we and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries. In connection with the extension, we converted the $100 million loan that Lilly previously provided to us into 2.5 million shares of our common stock.

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, 2007, we have earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. We amortized the $1.1 million license fee related to LY2181308 over a two-year period, which ended in June 2004. The two-year period corresponded to our period of performance for LY2181308 and there were no changes to the period of performance. In September 2004, we recognized $750,000 associated with the license fee we received for LY2275796. Lilly is responsible for the preclinical and clinical development of LY2275796 and we have no performance obligations for this drug. Our balance sheets as of December 31, 2007 and 2006 included deferred revenue of $156,000 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 royalties on future product sales of these drugs.

During 2007, we earned revenue from our relationship with Lilly totaling $402,000, compared to $1.2 million and $10.8 million for 2006 and 2005, 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 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. During 2007 and 2005, 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

Antisense Therapeutics Limited

In February 2008, ATL, an Australian company publicly traded on the Australian Stock Exchange that we previously licensed ATL1102 to, licensed ATL1102 to Teva Pharmaceutical Ltd. ATL1102 is currently in Phase 2 studies to assess the safety and activity of the drug in patients with multiple sclerosis. 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.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and sight disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we extended for an additional two years in January 2007. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide to ATL during the collaboration.

6. Collaborative Arrangements and Licensing Agreements (Continued)

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 balance sheets as of December 31, 2007 and 2006 include deferred revenue of $250,000 and $0, respectively. For the year ended December 31, 2007, we recorded revenue of $80,000 related to this collaboration compared to $652,000 and $698,000 for 2006 and 2005, respectively. As of December 31, 2007 and 2006, 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, 2007 and December 31, 2006 included a short-term investment at fair market value of $1.4 million and $1.3 million, respectively, related to this equity investment.

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. We have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain. At December 31, 2007, we owned less than 10% of Excaliard's equity and we have no significant remaining obligations to perform. In addition, we are eligible to receive development milestone payments and royalties on antisense drugs developed by Excaliard. During 2007, we recognized revenue of $1 million related to a gene target licensing fee.

Altair Therapeutics Inc.

In October 2007, Altair, a new venture capital-funded biotechnology company, was created to focus 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 ISIS 369645, an inhaled inhibitor of the IL-4/IL-13 signaling pathways for the treatment of asthma. Altair is solely responsible for the continued development of ISIS 369645. At December 31, 2007, we owned 18 percent of Altair in the form of preferred stock. 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 ISIS 369645 and other drugs arising out of the research collaboration progress. During 2007, we recognized revenue of $494,000 from our relationship with Altair.

Atlantic Healthcare (UK) Limited

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

6. Collaborative Arrangements and Licensing Agreements (Continued)

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 Healthcare in the form of equity. We have recognized a valuation allowance of $2 million to offset this asset as realization of this asset is uncertain. At December 31, 2007, we owned approximately 13% of Atlantic Healthcare's equity. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic Healthcare's request, we will attempt to identify a second-generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second-generation lead drug candidate. During 2007, we did not recognize any revenue from our relationship with Atlantic Healthcare.

ImQuest Pharmaceuticals, Inc.

In April 2006, we granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, we will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, we are entitled to a portion of the consideration received. During 2007 and 2006, we did not recognize any revenue from our relationship with ImQuest.

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 are used 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. We have recognized a valuation allowance of $1.5 million to offset this asset as realization of this asset is uncertain. At December 31, 2007 and 2006, we owned less than 10% of Achaogen's equity. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products. During 2007 and 2006, we did not recognize any revenue from our relationship with Achaogen.

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 consisting of $250,000 in cash and a $250,000 convertible note. We have recognized a valuation allowance of $250,000 to offset the

6. Collaborative Arrangements and Licensing Agreements (Continued)

convertible note and the resulting common stock of iCo as the realization of this asset is uncertain. iCo 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. We have recognized a full valuation allowance to offset the equity we received as realization of this asset is uncertain.

In December 2005, we entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased drug manufactured by us for $700,000. iCo made a $525,000 prepayment to us consisting of $175,000 in cash and a $350,000 convertible note. We have recognized a valuation allowance of $350,000 to offset the convertible note and the resulting common stock of iCo as the realization of this asset is uncertain. In December 2006, our obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid us the remaining balance of $175,000. In May 2006, we received 869,025 shares of iCo common stock for the conversion of the convertible notes for the upfront fee and the drug we manufactured. iCo's common stock is listed on the TSX Venture Exchange under the stock symbol "ICO". At December 31, 2007, we owned 10% of iCo's equity, compared to less than 10% at December 31, 2006. There was no deferred revenue as of December 31, 2007 and 2006. During 2007, we did not recognize any revenue from our relationship with iCo, compared to $550,000 and $250,000 in 2006 and 2005, respectively.

OncoGenex Technologies 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. We fund 35% of the costs of developing OGX-011. In exchange, we receive 35% of any revenue generated by OncoGenex for OGX-011.

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug and we have no 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, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, we further broadened our antisense drug development partnership 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 the preclinical and clinical development of the drugs and we have no 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 also pay us milestone payments totaling up to $5 million

6. Collaborative Arrangements and Licensing Agreements (Continued)

for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of December 31, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-427.

During 2007, 2006 and 2005, we earned revenue of $4,000, $1.2 million and $2.7 million, respectively, related to our collaboration with OncoGenex. Our balance sheets at December 31, 2007 and 2006 included a long-term investment of $1.5 million related to our equity investment in OncoGenex. While there is no readily determinable market value for these securities, there has been no indication that our investment in OncoGenex has been impaired. Accordingly, we believe that the carrying value of this investment is equal to or below its current fair market value. As of December 31, 2007 and 2006, our ownership interest in OncoGenex was less than 10%.

Technology Development Satellite Company Collaborations

Archemix

In August 2007, we and Archemix entered into a new 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 the mRNA-targeting aspect that antisense mechanisms, including RNAi, exploit. 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 that was 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 our drugs. During 2007, we recognized revenue of $250,000 related to the milestone payment we received.

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 developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable 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 either an exclusive or co-exclusive basis depending on the target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million and are payable by us upon the occurrence of specified development and regulatory events. As of December 31, 2007, we did not have an RNAi-based drug in clinical development. As part of the collaboration, each

6. Collaborative Arrangements and Licensing Agreements (Continued)

party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

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, 2007, we have earned a total of $31.5 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners, including $26.5 million resulting from Alnylam's sublicense of our technology to Roche, which we recognized in the third quarter of 2007.

During 2007, 2006 and 2005, we sold Alnylam stock resulting in aggregate net cash proceeds of $12.2 million. As of December 31, 2007, we no longer own any shares of Alnylam. During 2007, 2006 and 2005, we generated revenue from our relationship with Alnylam totaling $26.5 million, $750,000 and $3.7 million, respectively, representing 38%, 3% and 9%, 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 includes a cross-license of our respective splicing-related intellectual property with Ercole. We are combining 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 certain of our chemistry patents. Pursuant to the terms of the Note and Warrant Purchase Agreement, during 2003 and early 2004, we made cash payments to Ercole of $500,000 and $250,000, respectively, in exchange for a convertible note. We expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into Ercole stock upon Ercole's successful completion of a venture capital financing. We also have the option to make an additional equity investment in Ercole. During 2007, 2006 and 2005, 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 were amended and restated in May 2003, we licensed our novel antisense chemistry, Peptide Nucleic Acid, or PNA, 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 balance sheets at December 31, 2007 and 2006 included a long-term investment of $625,000 related to this equity investment. While there is no readily determinable market value for these securities, there has been no indication that our investment in Santaris has been impaired; accordingly, we believe that the carrying value of this investment is equal to or below its current fair market value. Our ownership interest in Santaris, which was formed in the merger of Pantheco and Cureon A/S, was less than 10% at December 31, 2007 and 2006. During 2007, 2006 and 2005, we did not recognize any revenue from our relationship with Santaris.

6. Collaborative Arrangements and Licensing Agreements (Continued)

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 2007 and 2006, we recognized revenue of $329,000 and $70,000, respectively, from our relationship with CHDI.

National Institutes of Health

In September 2007, we received a multi-year Phase 2 Small Business Innovation Research grant by the NIH for up to $1.5 million to design oligonucleotide drugs that can exploit the RNAi antisense mechanism for disease treatment. The Phase 2 grant builds upon a successfully completed Phase 1 program that demonstrated the feasibility of using single-stranded antisense drugs to target the RNAi pathway.

The multi-year grant will fund our research to improve the stability and tissue distribution of RNAi drugs. Much of the work will focus on optimizing the chemical properties of single-stranded oligonucleotides that trigger the RNAi pathway. In addition to demonstrating that compounds optimized with our chemistries produce superior results in animal models when compared to unoptimized compounds, the grant funds the discovery of RNAi-based drugs. During 2007, we recognized revenue of $119,000 related to this grant.

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, ISIS 325568 and ISIS 377131. In this transaction, we licensed to Symphony GenIsis the intellectual property related to our three drug programs, apoB-100, GCGR and GCCR. 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.

6. Collaborative Arrangements and Licensing Agreements (Continued)

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of 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 issuance, which was $7.14. 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. Using a Black-Scholes option-pricing model, we estimated the fair value of the warrant, at the grant date, to be $18.6 million. Our determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by our stock price, as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, our expected stock price volatility over the term of the warrant. 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 the warrant has 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 the warrant, specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

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 OMI, as part of the collaboration agreement with them, worldwide development and commercialization rights to the two diabetes drugs, ISIS 325568 and ISIS 377131, 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 calculations and does not affect our net loss.

In accordance with FIN 46R, we determined that prior to the acquisition in September 2007, Symphony GenIsis was a variable interest entity for which we were the primary beneficiary. As a result, we included the financial condition and results of operations of Symphony GenIsis in our consolidated financial statements. Our consolidated financial statements include the cash and cash equivalents held by Symphony GenIsis. Additionally, the consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Consolidated Balance Sheets, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis, less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by us to Symphony Capital. From the inception of the collaboration to the acquisition of Symphony GenIsis on September 27, 2007, this line item was reduced by Symphony GenIsis' expenditures, which were $46.2 million. The reductions to the "Noncontrolling Interest in Symphony GenIsis" on the Consolidated Balance Sheets are also recognized in our Consolidated Statements of Operations using a similar caption and reduce our net loss. For the years ended December 31, 2007 and 2006, our net loss was reduced by $23.2 million and $23.0 million, respectively.

6. Collaborative Arrangements and Licensing Agreements (Continued)

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 royalties and modest milestone payments 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 333611.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

In May 2001, we entered into an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. 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. In exchange for the license to Hybridon's antisense patents, we paid $15 million in cash and agreed to pay Hybridon $19.5 million in our common stock before May 2003. In return for access to our patents, Hybridon agreed to pay us $6 million in Hybridon common stock before May 2004. Our balance sheets at December 31, 2007 and 2006 reflected a licensing asset, net of amortization, of $15.7 million and $17.6 million, respectively. During 2004 and 2005, we sold all of our Hybridon stock for net proceeds of approximately $665,000. In September 2005, Hybridon changed its name to Idera Pharmaceuticals, Inc. During each of the years ended December 31, 2007, 2006 and 2005, we earned revenue of $10,000 related to our relationship with Hybridon.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, we expanded this license agreement to allow us to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees and will pay royalties on sales of the drugs utilizing the technology IDT licensed to us. During 2007 and 2005, we did not recognize any revenue from our relationship with IDT, compared to $20,000 in 2006.

Out-Licensing Arrangements; Royalty Sharing Agreements

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

6. Collaborative Arrangements and Licensing Agreements (Continued)

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 associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. 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 2007, 2006 and 2005, 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 Drug Royalty Trust 3. In October 2007, as a resolution for the various alleged competing breaches between us and DRT, DRT paid us $7 million, subject to the terms of an amendment to the original agreement, and an unaffiliated third party paid us $1 million as the final purchase price installment. 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 2007, 2006 and 2005, we recognized revenue of $7 million, $8 million and $7 million, respectively, under this arrangement.

As part of the sale, we agreed to pay DRT liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRT will receive a ten per cent per annum return, compounded quarterly on the total of all purchase price payments made by DRT to us through the default date minus the total of any royalties received by DRT through the default date. As of December 31, 2007, DRT has received royalties of $6.4 million. In addition, DRT may withhold any installment of the purchase price if immediately prior to such payment, we fail to meet a minimum liquidity requirement equal to the then outstanding balance on our loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRT has paid the impending purchase price installment; plus its cash burn over the most recent three months. 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 2007, 2006 and 2005, we recognized revenue of $807,000, $200,000 and $200,000, respectively, from our relationship with Roche Molecular Systems.

6. Collaborative Arrangements and Licensing Agreements (Continued)

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", "Tuschl IV" and "Esau" patents. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. Thereafter, we and Alnylam will share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. Regulus is operated 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 mutually agreed upon by us and Alnylam.

We transferred to Regulus certain funded research programs that will support Regulus' technology development goals. These programs include a grant from the Israel-U.S. Binational Industrial R&D Foundation, that supports research in the identification of a microRNA therapeutic for the treatment of HCV and a Small Business Innovation Research grant that supports further research for the miR-122 program.

Ibis Collaborations

We developed, within Ibis, the Ibis T5000 Biosensor System with substantial funding from government agencies. In particular, funding from the Defense Advanced Research Projects Agency of a multi-year collaboration with San Diego-based Science Applications International Corporation to identify infectious agents in biological weapons attacks made the initial development of the Ibis universal biosensor technology possible. A grant to Ibis from the Centers for Disease Control and Prevention furthered development and application of our Ibis technology to the surveillance of human infectious disease in the United Sates.

Under these programs, Ibis successfully demonstrated proof-of-principle of its biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. Many of our early government partners are now commercial customers of instruments, assay kits and/or assay services. We continue to work with government collaborators to further develop and expand the applications for the Ibis T5000 Biosensor System. Examples of these ongoing collaborations include:

- Ibis' grant from the National Institutes of Allergy and Infectious Diseases, or NIAID, a division of the NIH, for the development of applications to diagnose infectious diseases;

- Ibis' contract with the Defense Threat Reduction Agency, an agency within the Department of Defense, to advance sample preparation methodologies and validate applications on the Ibis T5000 Biosensor System for broad biological weapon detection;

- Ibis' contract with the NIAID to develop an Ibis T5000 application to specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates;

6. Collaborative Arrangements and Licensing Agreements (Continued)

- Ibis' subcontract with the University of Maryland School of Medicine to apply the Ibis T5000 technology to identify the causes of diarrheal diseases in developing countries; and

- Ibis' contract with the Department of Homeland Security Science and Technology Directorate, or DHS-S&T, for the advancement of Ibis' microbial forensics applications and the enhancement of Ibis' microbial database.

We are now commercializing the Ibis T5000 instrument, assay kits, and our assay services to both government and non-government customers.

Commercial Agreements

We plan to work with partners to manufacture, install and support Ibis T5000 instruments. In addition, our recent strategic alliance with Abbott provides Ibis with the necessary capital and focus to move quickly toward evolving Ibis toward larger commercial markets, such as clinical diagnostics.

Abbott Molecular Inc.

In January 2008, we, Ibis and Abbott entered into a strategic alliance master agreement pursuant to which:

- Abbott purchased Ibis common stock representing approximately 10.25% of the issued and outstanding common stock of Ibis for a total purchase price of $20 million;

- Ibis granted Abbott a subscription right to purchase an additional $20 million of Ibis common stock before July 31, 2008, which when combined with Abbott's initial investment would represent approximately 18.6% of the issued and outstanding common stock of Ibis;

- We granted Abbott an exclusive call option to acquire from us all remaining Ibis capital stock for a purchase price of $175 million, which, subject to Ibis satisfying a defined set of objectives, may be increased to as much as $190 million;

- If Abbott ultimately acquires Ibis under the call option agreement, Abbott will make the earn out payments described below, which will enable our shareholders to continue to benefit from Ibis' success.

The investment by Abbott provides Ibis the funding to take the key next steps in enhancing its value, while allowing it to remain independent and focused during the option period so as to best enable this progress. This alliance with Abbott also provides Ibis the benefit of an experienced partner in molecular diagnostics and will focus Ibis on commercial success.

If Abbott acquires from us all of the remaining Ibis capital stock under the call option, Abbott will pay us earn out payments equal to a percentage of Ibis' revenue related to sales of Ibis T5000 Biosensor Systems, including instruments, assay kits and successor products from the date of the final acquisition through December 31, 2025. These earn out payments will equal 5% of Ibis' cumulative net sales over $150 million and up to $2.1 billion, and 3% of Ibis' cumulative net sales over $2.1 billion. The earn out payments may be reduced from 5% to as low as 2.5% and from 3% to as low as 1.5%, respectively, upon the occurrence of certain events. In addition, as part of the final acquisition, Ibis may distribute to us, immediately prior to the closing, all of Ibis' cash on hand and any receivables or other payments due to Ibis under government contracts and grants held by Ibis as of the closing.

6. Collaborative Arrangements and Licensing Agreements (Continued)

The call option initially expires on December 31, 2008, provided that, subject to certain conditions, Abbott may extend the term of the call option through June 30, 2009. In addition, if Abbott does not exercise its subscription right by July 31, 2008, the call option will expire.

Until the expiration of the call option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis' capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. In addition, the strategic alliance contains a make whole provision such that in the event of a liquidation or change of control of Ibis, Abbott will receive a payment equal to the price paid per share of the capital stock of Ibis acquired by Abbott in the initial investment or under the subscription right, plus a yield of 3% annually from the date Abbott purchased the Ibis common stock, prior to the distribution of any proceeds to any other holders of Ibis capital stock.

Bruker Daltonics Inc.

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Under the agreement, Bruker Daltonics is the exclusive worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations, and service in North America, Europe, and the Middle East. In Europe and the Middle East, Bruker Daltonics will have exclusive rights to sell Ibis T5000 systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. Ibis has maintained worldwide marketing rights to the diagnostics market. By partnering with Bruker Daltonics, our goal was to eliminate the duplication of expenses associated with instrument development, manufacture, sales and service, and gain entry into the market much more rapidly than we could on our own. However, we believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have initiated the formal dispute resolution process under the agreement so that we can improve the manufacture, service and sales of our Ibis T5000 Biosensor Systems. Until we resolve our dispute with Bruker Daltonics, we will manufacture, sell and service our Ibis T5000 Biosensor Systems.

7. Segment Information and Concentration of Business Risk

Segment Information

We report our financial results in two reportable segments, Drug Discovery and Development, and our Ibis subsidiary. Segment loss from operations includes research and development, cost of commercial revenue for our Ibis subsidiary, selling, general and administrative expenses, and other charges attributable to the segment. Costs excluded from the segments consist of restructuring activities and prior to 2006, compensation benefit related to the variable accounting for stock options.

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, milestones and royalties. 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

7. Segment Information and Concentration of Business Risk (Continued)

optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Ibis subsidiary generates revenue from grants and contracts from United States government agencies, from sales of its Ibis T5000 Biosensor System and related assay kits and the analysis of samples within its assay services laboratory.

We do not include asset or liability information by reportable segment since we do not use the information for purposes of making decisions about allocating resources to the segments and assessing their performance.

The following is information for revenue and loss from operations by segment for the years ended December 31, 2007, 2006 and 2005.

Year ended December 31, 2007	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 22,319	$ 7,765	$ —	$ 30,084
Commercial revenue(1)	—	3,512	—	3,512
Licensing and royalty	36,025	—	—	36,025
Total segment revenue	$ 58,344	$ 11,277	$ —	$ 69,621
Loss from operations	$ (28,143)	$ (10,805)	$ —	$ (38,948)

Year ended December 31, 2006	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 5,418	$ 9,117	$ —	$ 14,535
Commercial revenue(1)	—	556	—	556
Licensing and royalty	9,441	—	—	9,441
Total segment revenue	$ 14,859	$ 9,673	$ —	$ 24,532
Loss from operations	$ (61,714)	$ (6,940)	$ 536	$ (68,118)

Year ended December 31, 2005	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 16,817	$ 11,793	$ —	$ 28,610
Licensing and royalty	11,523	—	—	11,523
Total segment revenue	$ 28,340	$ 11,793	$ —	$ 40,133
Loss from operations	$ (48,537)	$ (2,229)	$ (6,416)	$ (57,182)

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on our Consolidated Statements of Operations.

7. Segment Information and Concentration of Business Risk (Continued)

Concentrations of Business Risk

We have historically funded our operations in part from collaborations with corporate partners and as it relates to Ibis, from collaborations with various government agencies. Additionally, beginning in the second half of 2006, Ibis began selling commercial products and services. A relatively small number of partners historically have accounted for a significant percentage of our revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	2007	2006	2005
Partner A	38%	3%	9%
Partner B	19%	0%	0%
Partner C	10%	33%	17%
Partner D	5%	14%	9%
Partner E	6%	10%	4%
Partner F	1%	5%	27%
Partner G	1%	8%	14%

During 2007, 2006, and 2005, we derived approximately 16%, 39%, and 30%, respectively, of our revenue from agencies of the United States Government. In 2007, none of our significant partners were agencies of the United States Government. In 2006, two significant partners accounted for 14% and 10% of revenue from agencies of the United States Government and in 2005, one significant partner accounted for 14%.

Contract receivables from three significant partners comprised approximately 25%, 19% and 11% of contract receivables at December 31, 2007. Contract receivables from four significant partners comprised approximately 25%, 20%, 19% and 16% of contract receivables at December 31, 2006.

8. Restructuring Activities

For the year ended December 31, 2005, we recorded $7.0 million in costs associated with our restructuring activities resulting from our strategic decision to focus our resources on key programs. The 2005 charge for restructuring activities consisted of costs associated with a reduction in workforce of approximately 160 employees, the consolidation of our facilities in the United States, and the closure of our research and development laboratory in Singapore. In connection with the consolidation of our U.S. facilities, we completed the sale of the three buildings that we owned for a net gain of $1.5 million.

For the year ended December 31, 2006, we recorded a benefit of $536,000 associated with our restructuring activities. 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 had been 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 was previously accrued. These benefits were included in the restructuring activities for the year ended December 31, 2006.

8. Restructuring Activities (Continued)

Pursuant to SFAS 146, *Accounting for Costs Associated with Exit or Disposal Activities,* the following table sets forth the activity in the restructuring reserve.

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2005	$ 856	$ —	$ 765	$ 126	$ 1,747
Accrued and expensed	(282)	—	(265)	11	(536)
Charged against accrual	(574)	—	(500)	(137)	(1,211)
Balance at December 31, 2006	$ —	$ —	$ —	$ —	$ —

9. Employee Post Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($15,500 and $20,500 in 2007 for employees under 50 years old and over 50 years old, respectively). We made approximately $414,000, $362,000 and $404,000 in matching contributions for the years ended December 31, 2007, 2006 and 2005, respectively.

10. Legal Proceedings

On October 16, 2007, Idera (formerly Hybridon, Inc.) filed papers initiating an arbitration proceeding against us. Idera alleged that we improperly sublicensed certain Idera patents which were the subject of a Collaboration and License Agreement by and between Hybridon, Inc. and us dated May 25, 2001. This matter was arbitrated on December 4, 5 and 6, 2007. The arbitrator entered a final award on January 15, 2008 finding that we "acted wholly within our rights under the agreement in granting a sublicense to Alnylam." We have prevailed and this matter is closed.

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 have 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 have failed to achieve resolution of this dispute. Formal mediation efforts will be pursued immediately in an effort to avoid litigation.

11. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods.

11. Quarterly Financial Data (Unaudited) (Continued)

Summarized quarterly data for the years ended December 31, 2007, and 2006 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2007 Quarters				
Revenue	$ 2,450	$ 3,813	$ 38,631	$ 24,727
Operating expenses	23,351	23,473	28,574	33,171
Income (loss) from operations	(20,901)	(19,660)	10,057	(8,444)
Net loss applicable to common stock(1)	$ (13,020)	$ (11,024)	$ (105,304)	$ (6,957)
Basic and diluted net loss per share(1)(3)	$ (0.16)	$ (0.13)	$ (1.25)	(0.08)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2006 Quarters				
Revenue	$ 4,958	$ 4,375	$ 3,253	$ 11,946
Operating expenses(2)	20,974	21,477	21,517	28,682
Loss from operations(2)	(16,016)	(17,102)	(18,264)	(16,736)
Net loss applicable to common stock(2)	$ (17,480)	$ (2,172)	$ (12,105)	$ (14,146)
Basic and diluted net loss per share(3)	$ (0.24)	$ (0.03)	$ (0.16)	$ (0.18)

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

(2) Includes benefits related to restructuring activities of $0.5 million incurred during the year ended December 31, 2006.

(3) Net loss per share is computed 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.

QuickLinks

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

EXHIBIT 10.73

RESEARCH AGREEMENT

THIS RESEARCH AGREEMENT (this "*Agreement*"), dated as of October 22, 2007 (the "*Effective Date*"), is entered into by and between Isis Pharmaceuticals, Inc., a Delaware corporation ("*Isis*"), and CHDI, Inc., a New Jersey corporation (the "*Foundation*"). Isis and the Foundation will hereinafter be referred to individually as a "*Party*" and collectively as the "*Parties*".

The Foundation supports basic, applied and clinical research aimed at finding diagnoses, treatments, cures and preventions of Huntington Disease.

Isis is an RNA-based drug discovery and development company.

The Foundation and Isis desire to collaborate in the conduct of certain research and development activities related to Huntington Disease.

In consideration of the mutual representations, warranties and covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

Definitions

1. *Definitions*. For the purposes of this Agreement, the following terms have the meanings set forth below:

(a) "*ASO*" means an oligonucleotide compound, or analog thereof, having a sequence that is at least 6 bases long and that modulates expression of a gene target via the binding of such compound to a mRNA or pre-mRNA of such gene target.

(b) "*Bankruptcy Event*" means the (i) making of a general assignment for the benefit of creditors by an entity; (ii) filing of any petition by an entity or the commencement of any proceeding voluntarily by an entity for any relief under any bankruptcy or insolvency laws or any law relating to the relief of debtors; (iii) consent by an entity to the entry of an order in an involuntary bankruptcy or insolvency case; (iv) entry of an order or decree for relief against an entity by a court of competent jurisdiction in an involuntary case under any bankruptcy or insolvency laws or any law relating to the relief of debtors, which order or decree is unstayed and in effect for a period of ninety (90) consecutive days; (v) appointment, with or without the consent of an entity, of any receiver, liquidator, custodian, assignee, trustee, sequestrator or other similar official of an entity or any substantial part of its property; or (vi) admission by an entity in writing of its inability to pay its debts generally as they become due.

(c) "*Confidential Information*" means (i) the terms and conditions of this Agreement and (ii) all information (A) provided by one Party (the "*Disclosing Party*") to another Party (the "*Receiving Party*") that is clearly marked or identified as "Confidential" by the Disclosing Party at the time of disclosure or (B) specifically deemed to be "Confidential Information" pursuant to *Section 12(c)(i)* of this Agreement. If such transmittal occurs orally, the Disclosing Party will promptly reduce such transmittal to writing, mark and identify it as confidential, and provide such record to the Receiving Party. Specifically excepted from Confidential Information is all information that: (1) was previously known by the Receiving Party other

than by reason of disclosure by the Disclosing Party; (2) is publicly disclosed either prior to or subsequent to the Receiving Party's receipt of such information except by breach of this Agreement; (3) is rightfully received by the Receiving Party from a third party without an obligation of confidence to the Disclosing Party; or (4) is independently developed by the Receiving Party without use or reliance upon Confidential Information provided by the Disclosing Party.

(d) "*Control*" or "*Controlled*" means possession by Isis of the ability to grant a license or sublicense hereunder to an item of Isis Background Intellectual Property without violating the terms of any agreement between Isis and a third party.

(e) "*Foundation Background Intellectual Property*" means (i) all Intellectual Property (including Intellectual Property relating to any Foundation Provided Materials) (A) owned or licensed by the Foundation as of the Effective Date or (B) acquired or licensed by the Foundation from a third party (but excluding Isis) after the Effective Date; (ii) all Intellectual Property conceived, discovered, invented, made or first reduced to practice by, or on behalf of, the Foundation after the Effective Date (other than in the course of Isis' conduct of the Project); and (iii) all improvements, variations, modifications or enhancements of the Intellectual Property described in (i) and (ii) above conceived, discovered, invented, made or first reduced to practice by, or on behalf of, the Foundation after the Effective Date (including any such improvements, variations, modifications or enhancements conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis in the course of Isis' conduct of the Project).

(f) "*Foundation Collaborators*" means those third parties to whom the Foundation grants the right to use all or part of the Project Deliverables, Project Intellectual Property or Project Results for HD Research and Development, including any entity collaborating with the Foundation in the conduct of HD Research and Development and/or fee for service laboratories providing services to the Foundation in the furtherance of the Foundation's conduct of HD Research and Development.

(g) "*Foundation Provided Materials*" means the physical samples of cell lines, compounds, reagents and other materials, in each case as specified in the Project Description (i) to be provided to Isis by, or on behalf of, the Foundation or (ii) acquired by Isis from a third party at the express direction of the Foundation and for which the Foundation reimburses Isis in accordance with *Section 5(a)(ii)* of this Agreement, in each case to enable Isis to conduct the Project.

(h) "*Foundation Provided Material Information*" means all information relating to a Foundation Provided Material that is provided to Isis by, or on behalf of, the Foundation.

(i) "*HD Field of Use*" means any activity useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington Disease.

(j) "*HD Research and Development*" means any activity useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington Disease other than (i) the manufacture or distribution of any such product or service for sale or (ii) the sale of any such product or service. For the avoidance of doubt, HD Research and Development will not include any right to (A) manufacture or distribute any such product or service for sale or (B) sell any such product or service.

(k) "*High Q Research Group*" means the community of investigators and organizations funded by the Foundation and its affiliates whose objective is to find diagnoses, treatments, cures and preventions of Huntington Disease.

(l) "*Huntington*" means the human gene known as IT15 or HD (GenBank accession #NM_002111.5), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

(m) "*Huntington Disease*" means the hereditary disorder caused by mutation associated with trinucleotide repeat expansion in the Huntington gene on chromosome 4p.

(n) "*Intellectual Property*" means any discovery, invention, formulation, know-how, trade secret, method, technological development, enhancement, modification, improvement, work of authorship, computer software (including, but not limited to, source code and executable code) and documentation thereof, data or collection of data, whether patentable or not, or susceptible to copyright or any other form of legal protection.

(o) "*Isis Background Intellectual Property*" means (i) all Intellectual Property (excluding any Pre-Project Compound Intellectual Property) (A) owned or licensed by Isis as of the Effective Date or (B) acquired or licensed by Isis from a third party (other than the Foundation) after the Effective Date; (ii) all Intellectual Property conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis on or after the Effective Date other than in the course of Isis' conduct of the Project; and (iii) all improvements, variations, modifications or enhancements of the Intellectual Property described in (i) and (ii) above conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis after the Effective Date (including any such improvements, variations, modifications or enhancements conceived, discovered, invented, made or first reduced to practice by, or on behalf of, Isis in the course of Isis' conduct of the Project).

(p) "*Isis Provided Materials*" means any mice and the physical samples of compounds, reagents, cell lines and other materials acquired by Isis from a third party to enable Isis to conduct the Project.

(q) "*Isis Provided Reimbursable Materials*" means those Isis Provided Materials specified in the Project Description for which the Foundation will reimburse Isis in accordance with *Section 5(a)(ii)* of this Agreement.

(r) "*MOE Gapmer*" means a single-stranded ASO of less than 25 nucleotides comprising a region of at least 6 unsubstituted 2' deoxy nucleotides with the remaining nucleotides having a 2'-O-(methoxyethyl) substitution at the 2' position.

(s) "*Patent Expenses*" means all out-of-pocket costs and expenses (including attorneys' fees and government filing fees) incurred in connection with the preparation, filing, prosecuting and maintenance of the filings to protect the Parties' rights in any Project HD Intellectual Property.

(t) "*Patentable Project HD Intellectual Property*" means any Project HD Intellectual Property which is or may be patentable or otherwise protectable under Title 35 U.S.C. and corresponding legislation in other jurisdictions.

(u) "*Phase*" means a distinct stage of the Project encompassing definitive scientific research and/or development activities as set forth in the Project Description.

(v) "*Pre-Project Compound*" means any MOE Gapmer identified by Isis prior to the Effective Date in the course of Isis' conduct of research activities pursuant to that certain Research Agreement, dated as of August 1, 2006, entered into between Isis and the Foundation which is used in Isis' conduct of the Project.

(w) "*Pre-Project Compound Intellectual Property*" means any Intellectual Property in or relating to a Pre-Project Compound.

(x) "*Project*" means the program of scientific research and development of one or more Project Compounds, to be conducted by Isis as described in the Project Description.

(y) "*Project Compound*" means any (i) Pre-Project Compound or (ii) MOE Gapmer that is identified by Isis in the course of Isis' conduct of the Project, including any Project Human Compound. For the avoidance of doubt, Pre-Project Compounds will be Project Compounds for all purposes under this Agreement.

(z) "*Project Deliverable*" means (i) those Project Reports (as defined in *Section 4(e)* of this Agreement) and other items set forth in the Project Description which are to be delivered by Isis to the Foundation in connection with the conduct of the Project by Isis and (ii) those Project Compounds delivered by Isis to the Foundation pursuant to a Project Compound Request Notice under *Section 2(d)* of this Agreement.

(aa) "*Project Description*" means the written document attached to this Agreement as *Appendix A* describing the activities to be undertaken by Isis to conduct and complete the Project.

(bb) "*Project HD Intellectual Property*" means any Project Intellectual Property that (i) claims the use of a Project Compound for the treatment of Huntington Disease or (ii) is useful for the creation, development, manufacture or distribution of a product or service for the diagnosis, treatment, cure or prevention of Huntington Disease.

(cc) "*Project Human Compound*" means any Project Compound that modulates the expression of Huntington and acts predominantly by hybridizing to mRNA or pre-mRNA in humans.

(dd) *Project Intellectual Property*" means any (i) Pre-Project Compound Intellectual Property and (ii) Intellectual Property conceived, discovered, invented, made or first reduced to practice in the course of Isis' conduct of the Project other than any such Intellectual Property that constitutes Isis Background Intellectual Property or Foundation Background Intellectual Property.

(ee) *Project Non-HD Intellectual Property*" means any Project Intellectual Property that does not constitute Project HD Intellectual Property.

(ff) "*Project Non-Human Compound*" means any Project Compound that does not constitute a Project Human Compound.

(gg) "*Project Results*" means any data, formulae, methods, outcomes, protocols or other results produced in the course of Isis' conduct of the Project (including any animal models, cell lines, compounds, Project Compounds, reagents or other materials).

(hh) "*Third Party Results*" means any data, formulae, methods, outcomes, protocols or other results (i) produced in the course of research conducted by members of the High Q Research Group (other than Isis) and (ii) funded by the Foundation or one of its affiliates.

(ii) "*Research and Development*" means any activity useful for the creation, development, manufacture or distribution of a product or service other than (i) the manufacture or distribution of any such product or service for sale or (ii) the sale of any such product or service. For the avoidance of doubt, Research and Development will not include any right to (A) manufacture or distribute any such product or service for sale, or (B) sell any such product or service.

(jj) "*Specialized Third Party Licenses and Services*" means those specialized (i) third party licenses which are necessary for Isis to possess and use a unique reagent, cell line, compound or other material to conduct the Project as agreed upon by the Steering Committee (as defined in *Section 4(a)(ii)* of this Agreement) or (ii) specialized services to be performed by a third party which are necessary to enable Isis conduct the Project as agreed upon by the Steering Committee.

2. *Experimental Nature of the Project; Conduct of the Project; Certain Notifications Relating to the Research Project; Limited Right to Subcontract; Authority to Conduct each Phase of the Project; Election by the Foundation to Discontinue Funding of the Research Project*.

(a) *Experimental Nature of the Project*. The Foundation acknowledges that the Project is of an experimental and developmental nature, and accordingly, while Isis agrees to use its commercially reasonable efforts to complete the Phases of the Project authorized by the Foundation, Isis makes no representations or warranties that any particular or specific results or outcomes will be achieved or that the Project will be completed within the time frame specified in the Project Description, or at all.

(b) *Conduct of the Project; Certain Notifications Relating to the Research Project; Limited Right to Subcontract*.

(i) *Conduct of the Project*. Isis will devote such resources (including all necessary personnel, equipment, tools, Isis Provided Materials and supplies) and effort as is commercially reasonable to (i) conduct the Project in accordance with (A) this Agreement and (B) the Project Description and (ii) complete the Phases of the Project authorized by the Foundation within the time frames specified in the Project Description.

(ii) *Certain Notifications Relating to the Research Project*. If at any time (A) Isis makes a good faith determination that (1) the Project cannot be conducted substantially in accordance with (x) this Agreement and (y) the Project Description; (2) the Project cannot be completed within the time frames or budget set forth in the Project Description; or (3) the continued conduct of the Project in accordance with (x) this Agreement and (y) the Project Description is unlikely to yield scientifically valid or useful results or (B) the representations and warranties of Isis set forth in *Section 14(b)(i)* or *Section 14(b)(ii)* of this Agreement are not true and correct as of any date following the Effective Date (specifically including any instances during the course of the Project where Isis and the Foundation desire to pursue Project HD Intellectual Property and/or Project Compound(s) that are known or believed to require the practice or use of third party Intellectual Property which Isis does not have a license to practice or use, in which case the Foundation and Isis will meet and confer to determine the appropriate course of action), Isis will promptly give notice (a "*Change of Circumstances Notice*") to the Foundation.

(iii) *Limited Right to Subcontract*. Isis may subcontract the research activities set forth in *Appendix B-1* to be conducted as part of the Project (any such research activities hereinafter referred to as the "*Subcontracted Research Activities*") to such third-party subcontractors agreed upon by the Steering Committee to perform such Subcontracted Research Activities (each such third party hereinafter referred to as a "*Subcontractor*"). Isis hereby agrees that (1) each Subcontractor will agree in writing to conduct such activities in accordance with, and subject to, the terms and conditions of a subcontract (each such subcontract hereinafter referred to as a "*Subcontract Agreement*") approved in writing by the Foundation, (2) Isis shall not amend a Subcontract Agreement without the prior written consent of the Foundation, (3) Isis will endeavor to cause each Subcontractor to conduct such activities in accordance with, and subject to, the terms and conditions of this Agreement and the applicable Subcontract Agreement and (4) Isis will be solely responsible for ensuring the proper performance of any such activity conducted by each Subcontractor as if such activity were conducted by Isis.

(c) *Authority to Conduct each Phase of the Project; Election by the Foundation to Discontinue Funding of the Project*.

(i) *Authority to Conduct each Phase of the Project*. Isis will not proceed to conduct Phase 2 of the Project under this Agreement without the prior written consent of the Foundation. The Parties hereby acknowledge and agree that the execution and delivery of this Agreement by the Foundation will constitute the written consent of the Foundation for Isis to conduct only Phase 1 of the Project.

(ii) *Election by the Foundation to Discontinue Funding of the Project*. Within 30 days following the meeting of the Steering Committee held following delivery by Isis of the [***] of this Agreement) relating to the [***], the Foundation will have the right to elect to not provide funding for the conduct of subsequent Phases of the Project by giving written notice (a "*Funding Discontinuation Notice*") to Isis to such effect.

(d) *Project Compound Request Notice; Supply of Project Compounds by Isis*. Following the completion of the [***] of the Project, the Foundation will have the right, from time to time until [***] (the "*Request Period*"), to request that Isis supply the Foundation with Project Compounds for the sole purpose of enabling the Foundation to have the Foundation Collaborators conduct HD Research and Development by providing written notice to Isis to such effect (each, a "*Project Compound Request Notice*"). Each Project Compound Request Notice will specify the Project Compound and required amount thereof to be provided by Isis. Upon the receipt of a Project Compound Request Notice during the Request Period, Isis will use reasonable commercial efforts to (A) manufacture each Project Compound in accordance with the standards and specifications developed for such Project Compound during the course of the conduct of the Project and (B) supply the Foundation with the Project Compounds requested in such Project Compound Request Notice within a reasonable period of time. The Foundation will pay Isis a fee of $[***] per [***] (or portion thereof) per Project Compound requested by the Foundation, with a minimum order quantity per Project Compound of [***]. For the avoidance of doubt, Project Compounds supplied by Isis under this *Section 2(d)* will not be used by the Foundation or any Foundation Collaborator in humans, and until such time as the Parties enter into a written clinical use and supply agreement the Foundation and the Foundation Collaborators will in no event use a Project Compound in humans.

3. *Foundation Provided Materials; Reimbursement for Isis Provided Reimbursable Materials; Retention of Isis Provided Reimbursable Materials; Reimbursement for Specialized Third Party Licenses and Services*.

(a) *Foundation Provided Materials.*

(i) *Obligation to Provide Foundation Provided Materials and Foundation Provided Material Information*. The Foundation will be responsible for all aspects of acquiring and providing to Isis sufficient amounts of the Foundation Provided Materials together with the Foundation Provided Material Information related thereto as is specified in the Project Description. The Foundation hereby represents and warrants that the Foundation will have the right to transfer, or cause to be transferred, to Isis for the purposes of the conduct of the Project all such Foundation Provided Materials and Foundation Provided Material Information. The Foundation hereby further represents and warrants that all such Foundation Provided Materials and Foundation Provided Material Information provided to Isis by, or at the direction of, the Foundation will be provided to Isis in compliance with all applicable federal, state, local and international laws, rules, regulations, orders and guidelines.

(ii) *Use and Ownership of Foundation Provided Material Information and Foundation Provided Materials*. The Foundation Provided Material Information and the Foundation Provided Materials (A) will be used by Isis for the sole purpose of conducting the Project and for no other purpose and (B) will not, without the written consent of the Foundation or as expressly specified in the Project Description, be transferred to any third party. Except to the extent required to enable Isis to conduct the Project, Isis will not, directly or indirectly, reverse engineer, deconstruct or in any way analyze or determine the identity, structure or composition of any Foundation Provided Materials or the properties thereof (chemical, biochemical, physical, biological or other). As between Isis and the Foundation, (1) the Foundation owns the Foundation Provided Material Information and Foundation Provided Materials and (2) Isis will have no ownership or other interest in any Foundation Provided Material Information or Foundation Provided Materials.

(iii) *Retention of Foundation Provided Materials*. Isis will retain all unused Foundation Provided Materials for a period (each, a "*Foundation Provided Materials Retention Period*") of [***] following the completion of the Project. During each Foundation Provided Materials Retention Period, Isis will, at the Foundation's request and expense, ship all or part of the unused Foundation Provided Materials subject to such Foundation Provided Materials Retention Period to the Foundation or to such third party as the Foundation will direct in writing. Upon the expiration of such Foundation Provided Materials Retention Period, Isis will appropriately discard or destroy all such unused Foundation Provided Materials.

(b) *Reimbursement for Isis Provided Reimbursable Materials; Retention of Isis Provided Reimbursable Materials*.

(i) *Reimbursement for Isis Provided Reimbursable Materials*. The Foundation will, in accordance with *Section 5(a)(iii)* of this Agreement, reimburse Isis for the actual costs incurred by Isis to procure any Isis Provided Reimbursable Materials; provided, however, if (A) the cost to procure any such Isis Provided Reimbursable Material was not expressly specified in the Project Description or (B) the cost to procure any such Isis Provided Reimbursable Material is more than [***] greater than the estimated cost of such Isis Provided Reimbursable Material as specified in the Project Description, Isis will not procure any such Isis Provided Reimbursable Material without the express written consent of the Foundation.

(ii) *Retention of Isis Provided Reimbursable Materials*. Isis will retain all unused Isis Provided Reimbursable Materials for a period (each, a "*Isis Provided Reimbursable Materials Retention Period*") of [***] following the completion of the Project. During each Isis Provided Reimbursable Materials Retention Period, Isis will, at the Foundation's request and expense, ship all or part of the unused Isis Provided Reimbursable Materials subject to such Isis Provided Reimbursable Materials Retention Period to the Foundation or to such third party as the Foundation will direct in writing. Upon the expiration of such Isis Provided Reimbursable Materials Retention Period, Isis will appropriately discard or destroy all such unused Isis Provided Reimbursable Materials.

(c) *Reimbursement for Specialized Third Party Licenses and Services*. The Foundation will, in accordance with *Section 5(a) (iv)* of this Agreement, reimburse Isis for the actual costs incurred by Isis to license or procure any Specialized Third Party Licenses and Services; provided, that (i) the Steering Committee has consented to Isis licensing or procuring such Specialized Third Party Licenses and Services and (ii) the terms and conditions upon which such Specialized Third Party Licenses and Services are to be licensed or procured have been approved in writing by the Foundation.

Project Management

4. *Steering Committee; Project Managers; Limited Authority of the Steering Committee and Project Managers; Project Reports; Recordkeeping*.

(a) *Establishment of a Steering Committee; Responsibilities of the Steering Committee*.

(i) *Establishment of a Steering Committee*. The Parties will establish within a reasonable period of time following the date hereof a committee (the "*Steering Committee*") which will comprise four members, two of which members will be designated by each Party. The Steering Committee will establish its own internal operating procedures and meeting schedule (such meetings to be held in person or by video or telephone conference as mutually agreed upon by the Steering Committee); provided, however, the Steering Committee will meet not more than two (2) weeks following delivery by Isis of the Interim Report relating to the completion of a Phase of the Project and otherwise not less than quarterly.

(ii) *Responsibilities of the Steering Committee*. The Steering Committee will, among other things, (A) oversee the coordination, implementation and conduct of the Project; (B) review the status and progress of the Project; (C) determine if changes are needed to the Project; (D) implement any approved changes to the Project; (E) review and discuss the Project Results and such other matters related to this Agreement and the Project as requested by either of the Parties and (F) facilitate on-going communications between the Parties. Any matter which requires a decision by, or the approval of, the Steering Committee under this Agreement will require the affirmative consent of each representative of the Steering Committee. At each meeting of the Steering Committee, one representative will be appointed to record and distribute the minutes of such meeting to be circulated between the Parties within a period of two weeks after the respective meeting.

(b) *Appointment of the Project Managers; Responsibilities of the Project Managers*.

(i) *Appointment of the Project Managers*. Promptly following the execution of this Agreement, each Party will appoint a project manager (each, a "*Project Manager*") to oversee the day-to-day coordination, implementation and conduct of the Project. The Project Managers will meet (by video or telephone conference) on at least a bi-weekly basis. Isis' Project Manager will keep the Foundation's Project Manager fully informed as to the status and progress of the conduct of the Project (including the status of the completion time frame of the Project as compared to the estimated completion time frame specified in the Project Description) and such other matters related to the Project as reasonably requested by the Foundation's Project Manager.

(ii) *Responsibilities of the Project Managers*. The Project Managers will, among other things, (A) oversee the coordination, implementation and conduct of the Project; (B) review the status and progress of the Project; (C) determine if changes are needed to the Project; (D) implement any approved changes to the Project; (E) review and discuss the Project Results and such other matters related to this Agreement and the Project as requested by either of the Parties and (F) facilitate on-going communications between the Parties.

(c) *Limited Authority of the Steering Committee and Project Managers*. For the avoidance of any doubt, neither the Steering Committee nor either Project Manager will have the power or authority to make any amendments to this Agreement including the Project Description.

(d) *Recordkeeping*. Isis will keep complete and accurate records of the conduct of the Project and of all Project Results and Project Deliverables. Such records (including all applicable

laboratory notebooks containing data, information or notations relating to the conduct of the Project) will be available at all reasonable times during normal business hours for inspection, examination or copying by or on behalf of the Foundation at the Foundation's expense upon five (5) business days prior notice. Isis will retain all such records, including all raw data, for a period of not less than [***] from the date of termination of this Agreement. During such [***] period, Isis will, at the Foundation's request and expense, ship all or part of such records to the Foundation or to such third party as the Foundation will direct in writing. Notwithstanding the foregoing, Isis may retain copies of all such records to allow Isis to exercise its rights and satisfy any of its obligations under this Agreement.

(e) *Project Reports*. Isis will deliver to the Foundation (i) interim project reports (each, an "*Interim Project Report*") on the conduct of the Project (A) within [***] following the end of each [***] during the Project and (B) within [***] of [***] and (ii) a final project report (the "*Final Project Report*" and, together with the Interim Project Reports, the "*Project Reports*") on the conduct of the Project promptly following the [***]. Each Project Report on the Project will provide (A) a summary of the status and progress of the conduct of the Project (including the status of the completion time frame of the Project as compared to the estimated completion time frame specified in the Project Description), (B) material developments and issues in respect of the conduct of the Project, (C) the information expressly required to be included in such Project Report as specified in the Project Description and (D) such other matters related to the Project as reasonably requested by the Foundation's Project Manager.

Payments

5. *Payment Schedule; Isis Provided Reimbursable Materials; Specialized Third Party Licenses and Services; Shipping and Insurance; Payment Remittance*.

(a) *Payment Schedule; Isis Provided Reimbursable Materials; Specialized Third Party Licenses and Services; Shipping and Insurance*.

(i) *Payment Schedule*. In full consideration of Isis' (A) conduct of the Project and (B) performance of its obligations under this Agreement, the Foundation will make payments to Isis as provided in, and subject to the terms and conditions of, this Agreement. The amount, timing and conditions of each payment to be made by the Foundation to Isis for the conduct of the Project will be set forth in the payment schedule (the "*Payment Schedule*") attached hereto as *Appendix B-2*.

(ii) *Reimbursement for Subcontracted Research Activities Costs*. In addition to the payments set forth in the Payment Schedule, the Foundation will, subject to *Section 2(b)(iii)* of this Agreement, reimburse Isis for the actual costs and expenses billed to Isis by a Subcontractor pursuant to the terms and conditions of the applicable Subcontract Agreement for the conduct of the Subcontracted Research Activities conducted pursuant to such Subcontract Agreement (collectively, the "*Subcontracted Research Activities Costs*").

(iii) *Isis Provided Reimbursable Materials*. In addition to the payments set forth in the Payment Schedule, the Foundation will, subject to *Section 3(b)(i)* of this Agreement, reimburse Isis for the actual costs incurred by Isis to procure any Isis Provided Reimbursable Materials.

(iv) *Specialized Third Party Licenses and Services*. In addition to the payments set forth in the Payment Schedule, the Foundation will, subject to *Section 3(c)* of this Agreement,

reimburse Isis for the actual costs incurred by Isis in connection with the Specialized Third Party Licenses and Services.

(v) *Shipping and Insurance*. In addition to the payments set forth in the Project Description, the Foundation will reimburse Isis for the actual costs (including carriage, customs duties and insurance costs) incurred by Isis in connection with the delivery of the Project Deliverables to the Foundation (or such third party specified by the Foundation).

(b) *Payment Remittance*. Subject to the terms and conditions of this Agreement, each payment to be made by the Foundation under this Agreement will be due and payable by the Foundation within [***] of the date of the receipt by the Foundation of the invoice issued by Isis for such payment. Each invoice delivered by Isis under this Agreement shall (i) reference the "RecID" number set forth in the footer of this Agreement and the footer of the applicable supplement to this Agreement and (ii) be itemized and contain detailed information in respect of the costs being billed under such invoice (including all relevant receipts for costs being reimbursed). All payments made by the Foundation under this Agreement will be paid by check in US Dollars and remitted to Isis at the address set forth in *Section 17* of this Agreement, Attention: Chief Accounting Officer.

Results

6. *Ownership of Project Results; Notification and Delivery of Project Results; Withdrawal of Project Results; Disclosure of Project Results Within the High Q Research Group; Disclosure of Third Party Results to Isis; Disclosure not to Constitute Publication; Disclosure of Project Results Outside the High Q Research Group; Ownership of Project Deliverables; Transfer of Title, Delivery and Transport of Project Deliverables; Transfers of the Project Deliverables*.

(a) *Ownership of Project Results*. Isis and the Foundation will own [***] all Project Results. The ownership of the Project Results will vest in the Parties in that manner immediately upon creation. Each Party hereby assigns to the other party sufficient right, title and interest in the Project Results to accomplish such ownership. Each of Isis and the Foundation hereby agrees that it will not sell or otherwise transfer its title to any Project Results to any third party unless such third party takes title to such Project Results (i) subject to the rights of the non-transferring party in such Project Results under this Agreement and (ii) assumes the obligations of the transferring party with respect to such Project Results under this Agreement.

(b) *Notification and Delivery of Project Results; Withdrawal of Project Results*.

(i) *Notification and Delivery of Project Results*. Isis will (A) inform the Foundation of all Project Results (through the Steering Committee meetings and the Project Reports) and (B) deliver a copy of all Project Results to the Foundation, in each case within a reasonable period of time following the conception, discovery, invention or production, as the case may be, of each such Project Result.

(ii) *Withdrawal of Project Results*. If at any time after informing the Foundation of Project Results pursuant to *Section 6(b)(i)* of this Agreement Isis determines that there is a reasonable scientific basis to conclude that such Project Results are not scientifically valid or accurate, Isis will promptly so notify the Foundation.

(c) *Disclosure of Project Results Within the High Q Research Group; Disclosure of Third Party Results to Isis; Disclosure not to Constitute Publication; Disclosure of Project Results Outside the High Q Research Group*.

(i) *Disclosure of Project Results Within the High Q Research Group*. The Foundation may disclose Project Results to any member of the High Q Research Group who has agreed in writing that each of the covenants applicable to Third Party Results set forth in *Section 6(c)(ii)(A)* through *Section 6(c)(ii)(D)* of this Agreement are also applicable with respect to any Project Results disclosed to such member, and such member of the High Q Research Group agrees to be bound by such covenants.

(ii) *Disclosure of Third Party Results to Isis*. With respect to any Third Party Results disclosed to Isis, Isis will, until such Third Party Results are published or otherwise made publicly available (except by breach of this Agreement):

(A) hold all Third Party Results in confidence so that the disclosure of the Third Party Results among members of the High Q Research Group does not constitute a public disclosure and so that the ability to patent the Third Party Results is preserved; provided, however, Isis will not be required to hold any Third Party Results in confidence if such Third Party Results (1) were previously known by Isis other than by reason of disclosure by the Foundation; (2) were publicly disclosed except by breach of this Agreement either prior to or subsequent to the receipt of such Third Party Results by Isis; (3) are rightfully received by Isis from a third party without an express obligation of confidence to the Foundation or the member of the High Q Research Group who discovered such Third Party Results; (4) are independently developed by Isis without use or reliance upon Third Party Results provided by the Foundation; or (5) are disclosed pursuant to any applicable federal, state, local or international law, or any judicial or government request, requirement or order, provided that Isis takes reasonable steps to provide the Foundation with sufficient prior notice in order to allow the Foundation to contest such request, requirement or order;

(B) discuss the Third Party Results only with those employees of Isis that are advised (1) of the confidential nature of the Third Party Results and (2) that the Third Party Results must not be shared with anyone outside of Isis until the Third Party Results are made publicly available;

(C) not publish or otherwise publicly disclose methods, data or other results which are derived using the Third Party Results without appropriate written permission; and

(D) to acknowledge other researchers appropriately if the Third Party Results have contributed to a publication or presentation of methods, data or other results which are derived using the Third Party Results (including the Project Results).

(iii) *Disclosure not to Constitute Publication*. It is the intention of the Foundation, Isis and the other members of the High Q Research Group that the sharing of Project Results and Third Party Results among members of the High Q Research Group is to be conducted in such a manner that such sharing will not constitute "disclosure" for patent purposes.

(iv) *Disclosure of Project Results Outside the High Q Research Group*. With respect to each Project Result disclosed by Isis to the Foundation, on and after the [***] of the date hereof (such date hereinafter referred to as the "*Disclosure Date*"), the Foundation will have the right to disclose such Project Result to any individual or organization without any restrictions unless prior to the Disclosure Date Isis notifies the Foundation that there

exists good reasons for such disclosure to be withheld for an additional [***] period, in which case the Disclosure Date will be extended for an additional [***] and the provisions of this *Section 6(c)(iv)* will apply to such new Disclosure Date.

(d) *Ownership of Project Deliverables; Transfer of Title, Delivery and Transport of Project Deliverables; Transfers of the Project Deliverables*.

(i) *Ownership of Project Deliverables*. As between the Foundation and Isis, the Foundation will own all Project Deliverables. Isis will have no ownership or other interest in any Project Deliverables. Isis hereby assigns, and agrees to assign, to the Foundation any and all right, title and interest of Isis in and to the Project Deliverables. Upon the written request of the Foundation, Isis will execute such documents and do all other acts and things as may be reasonably deemed necessary by the Foundation to effectuate and assure that all right, title and interest (except any right, title, or interest in any Intellectual Property embodied in or related to such Project Deliverable) of Isis in and to the Project Deliverables vest in the Foundation (or its designee). The Foundation will reimburse Isis for all reasonable out-of-pocket costs and expenses actually incurred by Isis to execute and deliver to the Foundation any such document(s) referred to immediately above. For the avoidance of any doubt, the ownership of a Project Deliverable by the Foundation does not grant any ownership rights to the Foundation in any Intellectual Property embodied in or related to such Project Deliverable as the ownership of any such Intellectual Property is governed solely by the terms of *Section 7* of this Agreement.

(ii) *Transfer of Title, Delivery and Transport of Project Deliverables*. Title to, and all risk in, each Project Deliverable will pass to the Foundation upon the delivery of such Project Deliverable to the delivery point specified by the Foundation in writing to Isis for such Project Deliverable. All Project Deliverables will be shipped to the delivery point specified by the Foundation in writing to Isis. The Foundation will reimburse Isis for the actual cost of transportation, shipping and insurance associated with the delivery by Isis of any Project Deliverables under this *Section 6(d)(ii)*.

(iii) *Transfers of the Project Deliverables to Foundation Collaborators*. The Foundation may transfer or have transferred the Project Deliverables to one or more of the Foundation's Collaborators; provided, that, any such Foundation Collaborator has entered into an agreement which requires them to maintain similar, but no less burdensome, obligations of confidentiality and non-use set forth in *Section 6(c)(i)* and *Section 12(a)(i)* of this Agreement. The Foundation and the Foundation Collaborators shall have the right to (A) use the Project Deliverables for HD Research and Development and (B) exercise the license rights granted by Isis pursuant to *Section 8* and *Section 10* of this Agreement.

Intellectual Property

7. *Ownership of Background Intellectual Property; Ownership of Project Intellectual Property; Disclosure of Inventions; Inventorship; Prosecution of Patentable Project HD Intellectual Property; Infringement or Misappropriation of Project Intellectual Property*.

(a) *Ownership of Background Intellectual Property.*

(i) *Ownership of Isis Background Intellectual Property*. As between the Foundation and Isis, Isis will own all Isis Background Intellectual Property. Except as expressly set forth in this Agreement, the Foundation will have no ownership or other interest in any Isis Background Intellectual Property.

(ii) *Ownership of Foundation Background Intellectual Property*. As between the Foundation and Isis, the Foundation will own all Foundation Background Intellectual Property. Isis

will have no ownership or other interest in any Foundation Background Intellectual Property.

(b) *Ownership of Project Intellectual Property; Grant of Exclusive License to the Project HD Intellectual Property by the Foundation Outside the HD Field of Use; Reversion of Foundation's Rights in Project HD Intellectual Property*.

(i) *Ownership of Project Non-HD Intellectual Property*. As between the Foundation and Isis, Isis will solely own all Project Non-HD Intellectual Property. Except as expressly set forth in this Agreement, the Foundation will have no ownership or other interest in any Project Non-HD Intellectual Property.

(ii) *Ownership of Project HD Intellectual Property*. Isis and the Foundation will own [***] all Project HD Intellectual Property. The Project HD Intellectual Property will vest in the parties in that manner immediately upon creation. Each Party hereby assigns to the other Party sufficient right, title and interest in the Project HD Intellectual Property to accomplish such ownership. Neither Party will sell or otherwise transfer its title to any Project HD Intellectual Property to any third party unless such third party takes title to such Project HD Intellectual Property (A) subject to the rights of the non-transferring party in such Project HD Intellectual Property under this Agreement and (B) assumes the obligations of the transferring party with respect to such Project HD Intellectual Property under this Agreement.

(iii) *Grant of Exclusive License to the Project HD Intellectual Property by the Foundation Outside the HD Field of Use*. The Foundation hereby grants to Isis an exclusive, paid-up, worldwide, license under any Project Intellectual Property to use the Project HD Intellectual Property for any use or purpose outside the HD Field of Use. The license rights granted by the Foundation under this *Section 7(b)(iii)* will be subject to termination by the Foundation in the event of Isis's material breach of this Agreement if such material breach is not cured within 45 days following receipt by Isis of notice of such material breach.

(iv) *Reversion of Foundation's Rights in Project HD Intellectual Property.*

(A) *Reversion of Foundation's Rights in Project HD Intellectual Property*. Upon the termination of this Agreement by the Foundation pursuant to *Section 15(b)(iv)* of this Agreement, subject to the rights reserved by the Foundation pursuant to *Section 7(b)(iv)(B)* of this Agreement, all of the Foundation's right, title and interest in and to the Project HD Intellectual Property will revert to Isis (the "*Reverted Project HD Intellectual Property*").

(B) *The Foundation's Right to Use Project Intellectual Property*. With respect to any Reverted Project HD Intellectual Property, the Foundation hereby reserves a non-exclusive, paid-up, irrevocable, perpetual license throughout the world for HD Research and Development including a non-exclusive license to (1) make, have made, use and have used products or processes resulting from such Reverted Project HD Intellectual Property, (2) practice and have practiced such Reverted Project HD Intellectual Property and (3) use and have used the Confidential Information relating to such Reverted Project HD Intellectual Property. The foregoing license (1) will be for HD Research and Development only, (2) will not include any right to manufacture or distribute for sale or sell, (3) will not be subject to royalties or other fees and (4) will include the right to grant sublicenses on the same terms; provided, that, such sublicense (i) is granted without payment of royalties, other fees or profit and (ii) prohibits the sublicensee from granting sublicenses.

(c) *Disclosure of Inventions; Inventorship.*

(i) *Disclosure of Inventions*. If either Party believes that any Project Intellectual Property has been conceived, discovered, invented, made or first reduced to practice in the course of Isis' conduct of the Project, such Party will promptly give notice (each, an "*Invention Notice*") of such Project Intellectual Property to the other Party.

(ii) *Inventorship*. The identity of the inventor of all Project Intellectual Property that is patentable will be determined in accordance with United States Patent law (or, if the jurisdiction in which patent or other protection is being sought does not permit the application of United States Patent law to identify the inventor, then in accordance with the applicable law in that jurisdiction).

(d) *Prosecution of Patentable Project HD Intellectual Property.*

(i) *Responsibility for Prosecution of Patentable HD Intellectual Property*. Isis will prepare, file, prosecute and maintain the appropriate filings for any Patentable Project HD Intellectual Property including (A) provisional patent applications or (B) patent applications (including a patent application corresponding to a previously filed provisional patent applications) claiming any such Patentable Project HD Intellectual Property in the United States and in such other jurisdictions as Isis and the Foundation jointly determine in good faith are necessary in order to protect Isis' and the Foundation's rights in such Patentable Project HD Intellectual Property. All such patent applications (including any patents issuing therefrom) covering inventions will be filed in the name of Isis and the Foundation as co-owners.

(ii) *Foundation Election to have Prosecution of Patentable Project HD Intellectual Property Initiated*. At any time and from time to time, the Foundation may elect to cause Isis to prepare, file, prosecute and maintain the appropriate filings for any Patentable Project HD Intellectual Property which is the subject of an Invention Notice by providing notice (a "*Foundation Patent Filing Notice*") of such election to Isis including (A) provisional patent applications or (B) patent applications (including a patent applications corresponding to a previously filed provisional patent applications) claiming any such Patentable Project HD Intellectual Property in the United States and in such other jurisdictions as Isis and the Foundation jointly determine in good faith are necessary in order to protect Isis' and the Foundation's rights in such Patentable HD Intellectual Property. All such applications will be filed in the name of Isis and the Foundation as co-owners.

(iii) *Covenants of Isis*. With respect to the prosecution and maintenance by Isis of any Patentable Project HD Intellectual Property pursuant to this *Section 7(d)*, Isis hereby agrees to use commercially reasonable efforts to promptly (A) give all notices required by, and comply with all other requirements of, applicable law to reasonably preserve the Parties' rights in such Patentable Project HD Intellectual Property as appropriate; (B) prepare, file, prosecute and maintain, as applicable, the appropriate filings to reasonably protect the Parties' rights in such Patentable Project HD Intellectual Property; (C) provide the Foundation with a copy of any provisional patent application or patent application filed claiming such Patentable Project HD Intellectual Property; (D) provide the Foundation with copies of all correspondence and other documents relating to the prosecution and maintenance of such Patentable Project HD Intellectual Property that come into the possession or control of Isis; and (E) such other documents and information related to such Patentable Project HD Intellectual Property as the Foundation may reasonably request and Isis can provide without incurring unreasonable cost and expense.

(e) *Disclaimer of Interest in Patentable Project HD Intellectual Property.*

(i) *Disclaimer Notice*. With respect to any Patentable Project HD Intellectual Property, either Party may, at any time, disclaim its interest in such Patentable Project HD Intellectual Property by providing notice of such election ("*Patentable Project HD Intellectual Property Disclaimer Notice*") to the other Party. Isis will be deemed to have disclaimed its interest in any Patentable Project HD Intellectual Property that is the subject of a Foundation Patent Filing Notice if Isis fails to comply with the obligations set forth in *Section 7(d)* of this Agreement with respect to such Patentable Project HD Intellectual Property.

(ii) *Effect of Disclaimer Notice*. In the event that a Patentable Project HD Intellectual Property Disclaimer Notice is delivered by either Party: (A) the disclaiming Party will promptly assign its ownership interest in the subject Patentable Project HD Intellectual Property to the non-disclaiming Party without consideration; (B) except as expressly set forth in *Section 8(f)* of this Agreement, the disclaiming Party will have no further rights to such Patentable Project HD Intellectual Property; and (C) the disclaiming Party hereby agrees at any time during and after the term of this Agreement to cooperate with the non-disclaiming Party without consideration but at the expense of the non-disclaiming Party in preparing, filing, prosecuting and maintaining, as applicable, the appropriate filings to protect the non-disclaiming Party's rights in such Patentable Project HD Intellectual Property, including obtaining execution by its employees of any documents necessary in connection with such activities. Each of the Parties hereby agrees to use reasonable efforts to keep the other Party advised of its deliberations regarding its determinations as to electing to disclaim its interest in any Patentable Project HD Intellectual Property.

(f) *Infringement or Misappropriation of Project Intellectual Property.*

(i) *Infringement or Misappropriation of Project Intellectual Property by Third Parties*. Each of Isis and the Foundation will promptly notify each other in writing of any alleged or threatened infringement or misappropriation of any Project Intellectual Property of which it becomes aware. In connection with any such alleged or threatened infringement or misappropriation, each of Isis and the Foundation will confer and take such action and allocate recoveries in such manner as they in good faith may mutually agree. Neither Isis nor the Foundation will settle a claim brought against a third party for such infringement or misappropriation without the consent of the other Party (such consent not to be unreasonably withheld, delayed, or conditioned).

(ii) *Infringement or Misappropriation Claims by Third Parties Related to Project Intellectual Property*. Each of Isis and the Foundation will promptly notify the other Party in writing if any third party alleges that the use or practice of any Project Intellectual Property infringes or misappropriate such third party's Intellectual Property rights. In connection with any such alleged infringement or misappropriation, each of Isis and the Foundation will confer and take such action in such manner as they in good faith may mutually agree. Neither Party will settle a claim brought by a third party in respect of such infringement or misappropriation without the consent of the other Party (such consent not to be unreasonably withheld, delayed, or conditioned).

8. *Licenses to Project HD Intellectual Property and Project Compounds in the HD Field of Use*.

(a) *Commercialization of Project HD Intellectual Property and Project Compounds; Reservation of Rights Regarding Project Intellectual Property and Project Compounds*.

(i) *Commercialization of Project HD Intellectual Property*. Except as expressly permitted by *Section 8(a)(ii)* of this Agreement, the use or other exploitation (including the grant of any license for any purpose) of any Project HD Intellectual Property or any Project Compound by either of the Parties or a third party for uses other than Research and Development in the HD Field of Use will only be done pursuant to the grant of a commercial license (any such license will hereinafter be referred to as a "*Commercial License*") pursuant to a license agreement executed by each of the Parties. For the avoidance of any doubt, the Parties agree that this Section 8 shall not apply to the use or other exploitation (including the grant of any license for any purpose) of any Project HD Intellectual Property outside the HD Field of Use.

(ii) *Reservation of Rights by the Parties to Grant Certain Licenses.*

(A) *Isis' Right to Use Project HD Intellectual Property and Project Compounds*. Isis hereby reserves the right to use any Project HD Intellectual Property and any Project Compound for all uses and purposes relating to Research and Development.

(B) *Isis' Right to Grant Research and Development Licenses*. Isis hereby reserves the right to grant non-exclusive licenses throughout the world to any Project HD Intellectual Property or any Project Compound for all uses and purposes relating to Research and Development.

(C) *Foundation's Right to Use Project HD Intellectual Property and Project Compounds*. The Foundation hereby reserves the right to use any Project HD Intellectual Property and any Project Compound for all uses and purposes relating to HD Research and Development.

(D) *Foundation's Right to Grant HD Research and Development Licenses*. The Foundation hereby reserves the right to grant non-exclusive licenses throughout the world to any HD Intellectual Property or any Project Compound for all uses and purposes relating to HD Research and Development.

(b) *Conduct of Human Clinical Trials.*

(i) *Obligation to the Parties to Confer*. Isis and the Foundation will confer with each other on the conduct of human clinical trials involving any Project Compound prior to the initiation of any human clinical trials for such Project Compound.

(ii) *Isis' Right to Conduct Human Clinical Trials*. Subject to *Section 8(b)(i)* of this Agreement, but notwithstanding any other provision of this Agreement, Isis will have the right to conduct human clinical trials involving any Project Compound.

(iii) *Foundation's Right to Conduct Human Clinical Trials*. Subject to *Section 8(b)(i)* of this Agreement, if (A) within [***] of the receipt of a request from the Foundation to undertake the conduct of a human clinical trial involving a Project Compound reasonably required to advance such Project Compound for the diagnosis, treatment, cure or prevention of Huntington Disease, Isis does not agree to promptly initiate and conduct such a human clinical trial or (B) the Parties decide that the Foundation will conduct human clinical trials concurrently with a human clinical trial being conducted by Isis, the Foundation will have the right to conduct human clinical trials on its own or through or with a third party selected by the Foundation. For the avoidance of doubt, the Foundation

will have the right to use Isis Background Intellectual Property, Project HD Intellectual Property and Project Compounds for the conduct of any such human clinical trials.

(c) *Consultations Between Isis and the Foundation Regarding Commercial Licenses; Third Party Proposals*.

(i) *Good Faith Consultations*. The Parties will consult, and work in coordination, with each other in accordance with the provisions of this *Section 8* concerning the grant of any Commercial License. With respect to any decision regarding the granting of any Commercial License, the Parties will (A) act in good faith and on a responsive basis and (B) make such decision on a reasonable basis using the principles and guidelines set forth in *Section 8(d)* of this Agreement.

(ii) *Right to Make Proposal Regarding the Granting of a Commercial License.*

(A) Either Party may submit to the Parties for their consideration under this *Section 8* a proposal for the granting of a Commercial License and the Parties will consult and make a determination regarding the granting of a Commercial License in respect of such proposal in accordance with the provisions of this *Section 8*.

(B) If (1) the Parties are evaluating multiple proposals (including one submitted by Isis pursuant to which Isis would be granted a Commercial License (the "*Isis Proposal*")) to determine whether or not the principles and guidelines set forth in this *Section 8* for the granting of a Commercial License have been satisfied and (2) more than one of such proposals (including Isis Proposal) satisfies the principles and guidelines set forth in this *Section 8* on a substantially equivalent basis, the Foundation will accept the Isis Proposal and grant a Commercial License to Isis in accordance with this *Section 8*.

(d) *Principles and Guidelines for Granting Commercial Licenses.*

(i) *Fundamental Principles and Guidelines*. A Commercial License will be granted if and only if the Parties mutually agree that the granting of such Commercial License is reasonably likely to:

(A) maximize the impact on the health and well-being of Huntington Disease patients;

(B) maximize the availability of diagnostic or therapeutic products to Huntington Disease patients; and

(C) maximize the speed of which diagnostic or therapeutic products are available to Huntington Disease patients.

(ii) *Availability of Products as Primary Factor for Granting Commercial Licenses*. Subject to *Section 8(d)(iii)* , if (A) the Parties are evaluating multiple proposals (including an Isis Proposal) for the granting of a Commercial License, (B) more than one of the proposals satisfies the principles and guidelines set forth in this *Section 8* (other than (1) the proposed economic terms and (2) the proposed time frame for making the diagnostic or therapeutic product which is to be the subject of such Commercial License available to Huntington Disease patients) on a substantially equivalent basis; and (C) one of the proposals sets forth a time frame for making the diagnostic or therapeutic product which is to be the subject of such Commercial License available to Huntington Disease patients that is substantially shorter than those set forth in the other proposals being considered by the Parties, the proposal setting forth such substantially shorter time frame will be accepted by the Parties and a Commercial License granted to the entity making such

proposal even if the economic terms of such proposal are substantially less than those set forth in the other proposals being considered by the Parties.

(iii) *Commercial License Agreement Terms and Conditions*. In addition to the principles and guidelines set forth in *Section 8(d)(i)* and *Section 8(d)(ii)* of this Agreement, a Commercial License will be granted if and only if the Parties mutually agree that the terms and conditions of the license agreement in respect of such Commercial License incorporates the following terms, principles and guidelines:

(A) reasonable performance milestones and a demonstrated capacity of the licensee to be able to meet those milestones; and

(B) reasonable business and other terms and conditions that are in keeping with the then existing market standards for agreements of such type and nature in respect of similar technology and in similar disease indications.

(e) *Resolution of Disputes Regarding the Granting of Commercial Licenses*. If the Parties do not reach a mutual agreement regarding the granting of a Commercial License in respect of a proposal for the granting of a Commercial License submitted by either of the Parties for their consideration in accordance with the provisions of this *Section 8*, the Parties hereby agree that the resolution of such disagreement will be determined in accordance with the dispute resolution procedures set forth in *Section 19* of this Agreement.

(f) *Reservation of Non-Exclusive Licenses of Disclaimed Patentable Project HD Intellectual Property*.

(i) *Reservation of Non-Exclusive License by the Foundation*. With respect to each patent (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of such patent or (B) any intellectual property rights claimed in respect of such patent) claiming Patentable Project HD Intellectual Property which the Foundation has disclaimed its interest pursuant to *Section 7(e)* of this Agreement, the Foundation hereby reserves a non-exclusive, paid-up, irrevocable, perpetual license throughout the world for HD Research and Development including a license to (1) make, have made, use and have used products or processes resulting from such Patentable Project HD Intellectual Property, (2) practice and have practiced such Patentable Project HD Intellectual Property and (3) use and have used the Confidential Information relating to such Patentable HD Intellectual Property. The foregoing license (a) will be for HD Research and Development only, (b) will not include any right to manufacture or distribute for sale or sell, (c) will not be subject to royalties or other fees and (d) will include the right to grant sublicenses on the same terms; provided, that, such sublicense (i) is granted without payment of royalties, other fees or profit and (ii) prohibits the sublicensee from granting sublicenses.

(ii) *Reservation of Non-Exclusive License by Isis*. With respect to each patent (including (A) any patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension or reissue in respect of such patent or (B) any intellectual property rights claimed in respect of such patent) claiming Patentable Project HD Intellectual Property which Isis has disclaimed its interest pursuant to *Section 7(e)* of this Agreement, Isis hereby reserves a non-exclusive, paid-up, irrevocable, perpetual license throughout the world for Research and Development including a license to (1) make, have made, use and have used products or processes resulting from such Patentable Project HD Intellectual Property, (2) practice and have practiced such Patentable Project HD Intellectual Property and (3) use and have used the Confidential Information relating to such Patentable HD Intellectual Property. The foregoing license (a) will be for Research and Development only, (b) will not include any right to manufacture or distribute for sale or sell, (c) will not be subject to royalties or other fees and (d) will include the right to grant sublicenses on the same terms; provided, that, such sublicense (i) is granted without payment of royalties, other fees or profit and (ii) prohibits the sublicensee from granting sublicenses.

(g) *Licenses to Isis Background Intellectual Property*. Subject to the disclosure set forth on *Schedule 14(b)(ii)(C)* , Isis will grant to any third party granted a Commercial License, in consideration for the amounts paid by such third party under such Commercial License a non-exclusive, license throughout the world to use Isis Background Intellectual Property Controlled by Isis, including a license under any related Intellectual Property rights Controlled by Isis (including any patent, patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension of reissue in respect of such patent), to the extent necessary to enable such third party to exploit the Project HD Intellectual Property as permitted by such Commercial License in accordance with the terms of this Agreement. Any license granted by Isis to a third party pursuant to this *Section 8(g)* shall terminate only in accordance with the terms and conditions of the Commercial License granted to such third party. For the avoidance of doubt, any license to Isis Background Intellectual Property granted under this *Section 8(g)* will in no event entitle a licensee under a Commercial License to use such Isis Background Intellectual Property to research, develop or otherwise use or make any compound other than the Project Compound(s) subject to such Commercial License.

9. *Non-Assert Covenants.*

(a) *Mutual Non-Assert Regarding Validity*. Each Party hereby undertakes not to challenge and not to assist others in challenging, and undertakes to ensure, by contract or otherwise, that its licensees and assignees of any Project Intellectual Property will not challenge nor assist others in challenging, the validity of any Project Intellectual Property.

(b) *Isis Non-Assert Regarding Infringement*. Isis hereby undertakes not to bring any action or assist others in bringing any action, and undertakes to ensure, by contract or otherwise, that its licensees and assignees of any Project Intellectual Property will not bring any action or assist others in bringing any action, against the Foundation or the Foundation's licensees or assignees of any Project HD Intellectual Property on the ground that the practice or use, as the case may be, of any Project HD Intellectual Property for HD Research and Development infringes or misappropriates the proprietary rights of Isis or Isis' licensees or assignees of any Project Intellectual Property.

(c) *Foundation Non-Assert Regarding Infringement*. The Foundation hereby undertakes not to bring any action or assist others in bringing any action, and undertakes to ensure, by contract or otherwise, that its licensees and assignees of any Project HD Intellectual Property will not bring any action or assist others in bringing any action, against Isis or Isis' licensees or

assignees of any Project Intellectual Property on the ground that the practice or use, as the case may be, of any Project Intellectual Property outside the HD Field of Use infringes or misappropriates the proprietary rights of the Foundation's or the Foundation's licensees or assignees of any Project HD Intellectual Property.

10. *Non-Exclusive License to Isis Background Intellectual Property*. Upon the request of the Foundation and subject to the disclosure set forth on *Schedule 14(b)(ii)(C)*, Isis will grant to the Foundation (or a third party designated by the Foundation, including a Foundation Collaborator) a non-exclusive, paid-up, world-wide license under any Isis Background Intellectual Property Controlled by Isis, including a license under any related Intellectual Property rights Controlled by Isis (including any patent, patent application, divisional, continuation, continuation-in-part, substitute, renewal, reexamination, extension of reissue in respect of such patent), to the extent necessary to enable the Foundation and the Foundation Collaborators to use the Project Results, any Project Deliverables and Project HD Intellectual Property and any Project Compound solely for HD Research and Development. The license rights granted by Isis under this *Section 10* will be subject to termination by Isis in the event of the Foundation's material breach of this Agreement if such material breach is not cured within 45 days following receipt by Isis of notice of such material breach. For the avoidance of doubt, any license to Isis Background Intellectual Property granted under this *Section 10* will in no event entitle a licensee to use such Isis Background Intellectual Property to research, develop or otherwise use or make any compound other than the Project Compound(s).

11. *Revenue Sharing.*

(a) *Revenue Sharing for Commercial Licenses*. All revenue ("*Revenue*") received by either of the Parties from the grant of any Commercial License (including a Commercial License pursuant to which Isis is the licensee) of any Project HD Intellectual Property (other than Project HD Intellectual Property which has been disclaimed by one of the Parties pursuant to *Section 7(e)* of this Agreement) will be distributed as follows:

(i) First, to Isis until an amount equal to the aggregate of the Patent Expenses paid by Isis has been received by Isis;

(ii) Second, to the Foundation and Isis equally until an amount equal to the aggregate of:

(A) the payments made by the Foundation to Isis under this Agreement (as amended from time to time) *plus*

(B) the payments made by the Foundation to third parties for the development of the Project HD Intellectual Property as a therapeutic product for Huntington Disease patients *plus*

(C) [***].

(iii) Thereafter, 100% to Isis.

(b) *No Revenue Sharing for Amounts Received by Isis for Research and Development of the Project HD Intellectual Property*. For the avoidance of doubt, this *Section 11* will only apply to amounts received pursuant to a Commercial License and will not apply to any amounts received by Isis so long as any such amounts are paid (x) solely to reimburse Isis for the actual internal costs and expenses incurred by Isis from the use of Project HD Intellectual Property for Research and Development conducted internally by Isis, or (y) for the use or other exploitation (including the grant of any license for any purpose) of any Project HD Intellectual Property outside the HD Field of Use.

Confidentiality; Trademarks

12. *Confidentiality and Non-Use; Use by Representatives; Exceptions to Confidentiality and Non-Use; Certain Information Deemed Confidential Information; Certain Information Specifically Excepted from Being Deemed Confidential Information*.

(a) *Confidentiality and Non-Use; Use by Representatives.*

(i) *Confidentiality and Non-Use*. Each Party will treat the Confidential Information of the other Party in the same manner as such Party would treat its own confidential or proprietary information. Without limiting the generality of the foregoing, and except to the extent expressly permitted by the terms and conditions of this Agreement, neither Party will, without the prior written consent of the other Party, (A) disclose the Confidential Information of the other Party to any third party or (B) use the Confidential Information of the other Party for any purpose.

(ii) *Use by Representatives*. Except as expressly permitted by the terms and conditions of this Agreement, each Party hereby agrees to limit disclosure of the other Party's Confidential Information to those of its directors, officers, employees, representatives, consultants and advisors (including legal counsel) who (A) have a need to know such Confidential Information to enable such Party to perform its obligations, or exercise its rights, under this Agreement and (B) have entered into an agreement which requires such representatives to maintain similar, but no less burdensome, obligations of confidentiality and non-use to those contained in this Agreement.

(b) *Exceptions to Confidentiality and Non-Use*. Either Party may, without the prior written authorization of the other Party, (i) disclose the Confidential Information of the other Party to the limited extent it is required to pursuant to any applicable federal, state, local, or international law, or any judicial or government request, requirement or order; provided, that, such Party provides the other Party with sufficient prior notice, and cooperates with the other Party (at such other Party's cost and expense), to allow the other Party to contest such request, requirement or order and (ii) disclose (A) the existence of this Agreement; (B) a general summary of the Project being conducted under this Agreement; (C) the aggregate dollar amount of fees to be paid by the Foundation under this Agreement; and (D) any specific terms of this Agreement that are a matter of public record except by breach of this Agreement.

(c) *Certain Information Deemed Confidential Information*. Subject to the exceptions in *Section 1(c)* of this Agreement, (i) all Project Intellectual Property and Project Results will be deemed Confidential Information of each of the Parties, (ii) all Isis Background Intellectual Property will be deemed Confidential Information of Isis and (iii) all Foundation Background Intellectual Property and Foundation Provided Material Information will be deemed Confidential Information of the Foundation.

13. *Use of Trademarks*. No Party will use the name, trademarks, logos, physical likeness or other symbol of the other Party (or their employees) for any marketing, advertising, public relations or other purposes without the prior written authorization of the other Party, except that either Party may make reference to the Foundation's funding of the Project, provided that, in any such reference, the relationship of the Parties will be accurately and appropriately described.

14. *Covenants; Representations and Warranties*

(a) *Covenants*. Isis hereby agrees to each of the following:

(i) *Conduct of the Project; Compliance with Law*. The Project will be conducted using generally accepted industry standards and practices. The Project will be conducted in compliance with all applicable federal, state, local, international, health authority and institutional laws, rules, regulations, orders and guidelines.

(ii) *Audit; Access*. At reasonably convenient times and dates and upon reasonable prior notice (in all cases at least 10 business days), (A) the Foundation and its representatives will have the right to audit Isis' compliance with this Agreement and (B) Isis will provide the Foundation and its representatives with reasonable access to the facilities used in the conduct of the Project, data and personnel in order to assess the progress of the Project being conducted by Isis.

(iii) *Project Team*. The Project will only be conducted by individuals who have agreed to assign any ownership or other rights they may acquire in any Project Intellectual Property conceived, discovered, invented or made in the conduct of the Project to Isis so that Isis may perform its obligations under this Agreement.

(iv) *Licenses and Approvals*. Isis has obtained all licenses, permits, consents and other approvals necessary for Isis to perform its obligations under this Agreement.

(v) *Conflicting Obligations*. Isis has not granted any right or entered into any agreement or understanding that conflicts with Isis' obligations or the Foundation's rights under this Agreement. Isis will not grant any right and will not enter into any agreement or understanding that conflicts with Isis' obligations or the Foundation's rights under this Agreement.

(vi) *Further Assurances*. Isis will execute such further documents, instruments, licenses and assurances and take such further actions as the Foundation may reasonably request from time to time to better enable the Foundation to exercise its rights under this Agreement; *provided, that,* such further documents, instruments, licenses, assurances and actions will not materially change either Party's rights or obligations under this Agreement.

(b) *Representations and Warranties*. Isis hereby represents and warrants to the Foundation the following as of the Effective Date:

(i) *General Intellectual Property*. To the knowledge of Isis, Isis owns or has the right to use pursuant to a valid and enforceable, written license, sublicense, agreement or other permission, all Intellectual Property necessary to conduct the Project. To the knowledge of Isis, except as specifically disclosed in that certain letter, dated as of the date hereof, from Grantland E. Bryce, Vice President, Legal & General Counsel to Robi Blumenstein, Isis' conduct of the Project does not interfere with, infringe upon, violate or misappropriate any Intellectual Property rights of any third party.

(ii) *Isis Background Intellectual Property*. To the knowledge of Isis, (A) *Schedule 14(b)(ii)(A)* sets forth a complete and accurate list of all Isis Background Intellectual Property Controlled by Isis that would be necessary to enable (1) a third party licensee under a Commercial License to practice any Project HD Intellectual Property to the extent necessary for such third party to commercialize one or more Project Compounds under a Commercial License in accordance with the terms of this Agreement and (2) the Foundation and the Foundation Collaborators to use the Project Results, any Project

Deliverables and Project HD Intellectual Property solely for HD Research and Development and (B) *Schedule 14(b)(ii)(B)* sets forth a complete and accurate list of all Isis Background Intellectual Property that is not Controlled by Isis that would be necessary to enable (1) a third party licensee under a Commercial License to practice any Project HD Intellectual Property to the extent necessary for such third party to commercialize one or more Project Compounds under a Commercial License in accordance with the terms of this Agreement and (2) the Foundation and the Foundation Collaborators to use the Project Results, any Project Deliverables and Project HD Intellectual Property solely for HD Research and Development. Except as set forth on *Schedule 14(b)(ii)(C)*, Isis has the right to grant licenses or sub-licenses to the Isis Background Intellectual Property set forth on *Schedule 14(b)(ii)(A)* and *Schedule 14(b)(ii)(B)* without obtaining the consent of any third party or the payment of any compensation to a third party.

Term; Termination; Effect of Termination

15. *Term; Termination of Certain Provisions; Facilitation of Continued Research; Effect of Termination of Certain Provisions*.

(a) *Term*. The term of this Agreement will commence on the date hereof and will continue in effect until terminated in accordance with the terms hereof or by the mutual written agreement of the Parties.

(b) *Termination of Certain Provisions by the Foundation*. The Foundation may, by giving notice to Isis, elect to terminate each of the sections specified in *Section 15(e)(i)* of this Agreement and discontinue the Project upon the occurrence and continuation of any of the following events:

(i) *Breach of this Agreement*. Isis (A) breaches any material representation, warranty or covenant given by it under this Agreement or (B) defaults in the performance of any of its material obligations under this Agreement and such breach or default is not remedied within 45 days of the receipt by Isis of notice of such breach or default from the Foundation.

(ii) *Change of Circumstances Notice*. Isis delivers a Change of Circumstances Notice to the Foundation.

(iii) *Foundation Determinations Regarding the Project*. The Foundation makes a good faith determination that (A) the Project cannot be conducted substantially in accordance with the Project Description; (B) the Project cannot be substantially completed within the time frame or budget set forth in the Project Description; or (C) the continued conduct of the Project in accordance with *Appendix A* is unlikely to yield scientifically valid or useful results.

(iv) *Project Discontinuation Notice*. The Foundation has delivered a Project Funding Discontinuation Notice to Isis in accordance with *Section 2(c)* of this Agreement.

(v) *Bankruptcy Event*. Isis becomes subject to a Bankruptcy Event.

(c) *Termination of Certain Provisions by Isis*. Isis may, by giving notice to the Foundation, elect to terminate each of the provisions specified in *Section 15(e)(i)* of this Agreement and discontinue the Project upon the occurrence and continuation of any of the following events:

(i) *Breach of this Agreement*. The Foundation (A) breaches any material representation, warranty or covenant given by it under this Agreement or (B) defaults in the performance of any of its material obligations under this Agreement and such breach or default is not

remedied within 45 days of the receipt by the Foundation of notice of such breach or default from Isis.

(ii) *Bankruptcy Event*. The Foundation becomes subject to a Bankruptcy Event.

(d) *Facilitation of Continued Research*. Upon any cancellation of the Project or the termination of this Agreement, if requested by the Foundation, Isis and the Foundation will, in good faith, discuss the use of reasonable efforts to facilitate the continuance of the Project elsewhere.

(e) *Effect of Termination of Certain Provisions.*

(i) *Termination of Specified Provisions; Survival of Remaining Provisions*. Immediately upon an election by the Foundation pursuant to *Section 15(b)* of this Agreement or by Isis pursuant to *Section 15(c)* of this Agreement, each of *Section 2(b)*, *Section 3(a)(i)*, *Section 3(b)(i)*, *Section 3(c)*, *Section 4(a)*, *Section 4(b)*, and *Section 5* will immediately terminate and have no further force or effect; provided, however, that, within 30 days of such termination, Isis will deliver a Final Project Report in respect of the Project then in process to the Foundation covering the period through the date of such termination and the Foundation will remit to Isis all undisputed amounts owed pursuant to *Section 2(b)(iii)*, *Section 3(b)(i)*, *Section 3(c)* and *Section 5* of this Agreement that were committed to by Isis in accordance with the terms of this Agreement or accrued prior to the effective date of such termination in accordance with *Section 5(b)* of this Agreement. The Parties hereby acknowledge and agree that in the event of the termination of the provisions specified in this *Section 15(e)(i)*, all other sections and provisions of this Agreement will survive indefinitely and remain in full force and effect.

(ii) *Effect of Termination*. The termination of the provisions specified in *Section 15(e)(i)* of this Agreement will not (A) relieve any Party then in breach of this Agreement for any liabilities to the other Party in respect of any breach under this Agreement or (B) relieve either Party from any of the obligations such Party may have to the extent such obligations accrued prior to the date of such termination or (C) relieve either Party from any of the obligations such Party may have under any of the sections or provisions of this Agreement that expressly survive any termination of this Agreement.

Miscellaneous

16. *Independent Contractor*. Isis is acting as an independent contractor and not an agent, joint venturer or partner of the Foundation. Nothing in this Agreement will create, evidence or imply any agency, partnership or joint venture between the Parties. Neither Party will act or describe itself as the agent of the other Party nor will it represent that it has any authority to make commitments on the other Party's behalf.

17. *Notices*. Any notice required or permitted to be given by this Agreement will be in writing and will be delivered by personal delivery, facsimile (provided the sender has evidence of successful transmission) or next day courier service. Any notice so delivered will be deemed to be given, delivered and received, if delivered by personal delivery, on the day of delivery and if delivered by facsimile or courier service, on the day following dispatch. All such notices are to be given or made to the Parties at the following addresses (or to such other address as any Party may designate by a notice given in accordance with the provisions of this section):

If to the Foundation to:

CHDI, Inc.
c/o MRSSI, Inc.
350 Seventh Avenue, Suite 601
New York, NY 10001
Attention: Ruth Basu
Telephone: 212-660-8102
Fax: 212-239-2101

If to Isis to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Frank Bennett
Telephone: 760-931-9200
Fax: 760-603-4650

With copies to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Executive Vice President & CFO
Telephone: 760-931-9200
Fax: 760-603-4650

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Vice President, Legal & General Counsel
Telephone: 760-931-9200
Fax: 760-268-4922

18. *Indemnity; Limitation on Damages.*

(a) *Indemnification by the Foundation*. The Foundation will defend and indemnify Isis, including, as applicable, its directors, officers, employees and agents, against any and all losses, costs and damages (including reasonable legal fees) suffered by Isis (and/or such other related persons)

in connection with any third party claim to the extent resulting from (i) the Foundation's negligence or willful misconduct; (ii) the Foundation's breach of this Agreement; or (iii) Isis' use or alleged use of any Foundation Provided Materials or Foundation Provided Material Information provided by the Foundation to Isis for the purpose of conducting the Project (but only to the extent such claim does not result from, or arise out of, an action for which Isis is obligated to indemnify the Foundation pursuant to *Section 18(b)* of this Agreement). For clarity, the Parties hereby agree that the parenthetical clause in the immediately preceding sentence is not intended to obviate or otherwise limit the possibility that both Isis and the Foundation may be determined to be joint tort-feasors and, therefore, share liability.

(b) *Indemnification by Isis*. Isis will defend and indemnify the Foundation, including, as applicable, its members, directors, officers, employees and agents, against any and all losses, costs and damages (including reasonable legal fees) suffered by the Foundation (and/or such other related persons) in connection with any third party claim to the extent resulting from (i) Isis' negligence or willful misconduct; (ii) Isis' breach of this Agreement; or (iii) the activities of Isis in the course of Isis' conduct of the Project including activities which infringe upon, violate, misappropriate or otherwise come into conflict with, or are alleged to infringe upon, violate, misappropriate or otherwise come into conflict with the Intellectual Property rights of a third party (but only to the extent such claim does not result from, or arise out of, an action for which the Foundation is obligated to indemnify Isis pursuant to *Section 18(a)* of this Agreement). For clarity, the Parties hereby agree that the parenthetical clause in the immediately preceding sentence is not intended to obviate or otherwise limit the possibility that both Isis and the Foundation may be determined to be joint tort-feasors and, therefore, share liability.

(c) *Limitation on Damages; Liability Cap.*

(i) *Limitation on Damages*. NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY OR ITS AFFILIATES FOR ANY CONSEQUENTIAL, SPECIAL, INDIRECT, INCIDENTAL, PUNITIVE OR EXEMPLARY DAMAGES OR OTHER SIMILAR OR LIKE DAMAGES (INCLUDING LOSS OF PROFITS) UNDER THIS AGREEMENT EVEN IF SUCH PARTY OR AFFILIATE HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

(ii) *Liability Cap*. Isis' liability to the Foundation under this Agreement shall not exceed [***]. The Foundation's liability to Isis under this Agreement shall not exceed $[***].

(d) *Indemnity Amounts*. The Parties hereby agree that any amounts owing pursuant to a Party's express indemnity obligations under this Agreement will not be subject to the limitation on damages restrictions set forth in *Section 18(c)* of this Agreement.

19. *Alternative Dispute Resolution*. If a dispute arises out of or relates to this Agreement, or breach thereof, the Parties agree first to try in good faith to settle such dispute, failing which such dispute will be settled by a single arbitrator in an arbitration in Denver, Colorado administered by JAMS under its Comprehensive Arbitration Rules and Procedures. The Parties will instruct the arbitrator that the prevailing party of any dispute (as determined by the arbitrator) will be awarded the reasonable attorneys' fees, costs and other expenses incurred by the prevailing party in the course of the arbitration of such dispute. The award rendered by the arbitrator will be final and binding on the Parties, and judgment on the award may be entered in any court having jurisdiction thereof if reasonably necessary for enforcement. The Parties agree that, notwithstanding anything to the contrary in such rules, any and all such proceedings will be confidential.

20. *Assignment*. Isis may not assign this Agreement without the prior written consent of the Foundation, except to an entity (a) that acquires all or substantially all of the business of Isis (whether by sale of assets or stock or by merger) and (b) who agrees, in writing, to assume Isis' obligations under this Agreement. Isis hereby agrees that any entity that acquires all or substantially all of the business of Isis (whether by sale of assets or stock or by merger) will (i) acquire Isis' interest in Isis Background Intellectual Property and (ii) agree, in writing, to assume "Isis' obligations under this Agreement. The Foundation may assign this Agreement so long as the assignee expressly assumes in writing the Foundation's obligations in this Agreement.

21. *Press Releases*. Upon execution of this Agreement, the Parties will mutually agree to issue either a joint press release or separate press releases announcing the existence of this Agreement, in any case in a form and substance agreed to in writing by the Parties. Each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed, *provided however*, that each Party may make disclosures permitted by, and in accordance with, *Section 12* of this Agreement. Each Party agrees to provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter thereof as soon as reasonably practicable under the circumstances prior to its scheduled release. Except under extraordinary circumstances, each Party will provide the other with an advance copy of any such announcement at least five business days prior to its scheduled release.

22. *Incorporation of Appendices, Supplements and Exhibits; Entire Agreement; Amendment*. The appendices, supplements and exhibits identified in this Agreement are incorporated herein by reference and made a part hereof. If anything in any appendix, supplement or exhibit attached to this Agreement or any notice, invoice or other document delivered by a Party under this Agreement conflicts with any terms or conditions set forth in the body of this Agreement, the terms and conditions set forth in the body of this Agreement will control. This Agreement constitutes the entire agreement among the Parties relating to the Project and all prior understandings and agreements relating to the Project are superseded hereby. This Agreement may not be amended except by a document signed by the each of the Parties.

23. *No Waiver*. Any failure of a Party to enforce any provision of this Agreement will not be deemed a waiver of its right to enforce such provision on any subsequent occasion. No waiver of any provision of this Agreement will be valid unless it is in writing and is executed by the Party against whom such waiver is sought to be enforced. A waiver by any of the Parties of any provision of this Agreement will not be construed to be a waiver of any succeeding breach thereof or of any other provision of this Agreement.

24. *Severability*. Whenever possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law. In the event a court of competent jurisdiction holds any provision of this Agreement to be invalid, such holding will have no effect on the remaining provisions of this Agreement, and they will continue in full force and effect.

25. *Interpretation; Headings*. The word "including" will mean "including without limitation". All pronouns and any variations thereof refer to the masculine, feminine or neuter, singular or plural, as the context may require. All terms defined in this Agreement in their singular or plural forms have correlative meanings when used herein in their plural or singular forms, respectively. Headings used in this Agreement are for convenience of reference only and are not intended to influence the interpretation hereof.

26. *Governing Law*. This Agreement will be governed by and construed in accordance with the domestic laws of the State of New York without giving effect to any choice or conflict of law

provision or rule (whether of the State of New York or any other jurisdiction) that would cause the application of the laws of any jurisdiction other than the State of New York.

27. *No Strict Construction*. The Parties have participated jointly in the negotiation and drafting of this Agreement. In the event of an ambiguity or question of intent or interpretation arises, this Agreement will be construed as if drafted jointly by the Parties, and no presumption or burden of proof will arise favoring or disfavoring any of the Parties by virtue of the authorship of any of the provisions of this Agreement.

28. *Counterparts*. This Agreement may be signed, including by facsimile signature, in two or more counterparts and each such counterpart will constitute an original document and such counterparts, taken together, will constitute the same instrument.

In witness to the foregoing, the Parties have executed this Research Agreement as of the date first written above.

Foundation:

CHDI, Inc.

By: /s/ ROBI BLUMENSTEIN

Name:
Title:

Isis:

Isis Pharmaceuticals, Inc.

By: /s/ B. LYNNE PARSHALL

Name:
Title:

Appendix A to Research Agreement

(Project Description)

[***]

Appendix B-1 to Research Agreement

(Subcontracted Research Activities)

[***]

Appendix B-2 to Research Agreement

(Payment Schedule)(1)

[***]

(1) See also attached corresponding Project Budget.

Schedule 14(b)(ii)(A) to Research Agreement

(Isis Background Intellectual Property Controlled by Isis)

[***]

Schedule 14(b)(ii)(B) to Research Agreement

(Isis Background Intellectual Property Not Controlled by Isis)

[***]

Schedule 14(b)(ii)(C) to Research Agreement

(Third-Party Consents; Third-Party Compensation)

[***]

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Ibis Biosciences, Inc., a Delaware Corporation

Isis Pharmaceuticals Singapore Pte Ltd., a Singapore Limited Private Company

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Regulus Therapeutics LLC, a Delaware Limited Liability Company

Symphony GenIsis, Inc., a Delaware Corporation

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Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777) of Isis Pharmaceuticals, Inc. and the related Prospectus of our reports dated March 11, 2008, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in the Annual Report (Form 10-K) for the year ended December 31, 2007.

/s/ ERNST AND YOUNG

San Diego, California
March 11, 2008

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Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: March 14, 2008

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

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Exhibit 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: March 14, 2008

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

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Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc. (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2007, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: March 14, 2008

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

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