UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2008

Commission file number 0-19125

Isis Pharmaceuticals, Inc.
(Exact name of Registrant as specified in its charter)

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

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

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

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

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

Common Stock, $.001 Par Value

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

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

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

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

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

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

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

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

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

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement for the fiscal year ended December 31, 2008 to be filed on or about April 6, 2009 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 2, 2009 are incorporated by

reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 63 to 66 incorporates several documents by reference as indicated therein.

* Excludes 27,845,955 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 2008. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

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FORWARD-LOOKING STATEMENTS

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

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

TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

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

Vitravene® is a registered trademark of Novartis AG.

CORPORATE INFORMATION

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

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PART I

Item 1. Business

Overview

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

commercial potential of these inventions, such as our Ibis Biosciences, Inc. subsidiary, which we recently sold to Abbott Molecular Inc., or AMI, a wholly owned subsidiary of Abbott Laboratories. All of these aspects fit into our unique business model and create continued shareholder value.

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

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

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

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

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

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

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

2008 and Early 2009 Business Highlights

Pipeline Highlights

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

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

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

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

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

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

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

- OncoGenex is evaluating OGX-011 in multiple Phase 2 studies in prostate, lung and breast cancer.
  - OncoGenex has reported encouraging data on OGX-011, including recent Phase 2 data that showed OGX-011 provided an overall survival advantage when combined with standard first-line chemotherapy in prostate cancer patients compared to standard first-line chemotherapy alone.
  - Previously reported data has shown better than expected survival when OGX-011 was combined with second-line chemotherapy as well as reduced levels of clusterin, OGX-011's target, and demonstrated durable reduction in pain and a decline in levels of PSA, a protein that is often elevated in patients with prostate cancer.
  - OncoGenex reported survival data on OGX-011 from a Phase 1/2 study in patients with NSCLC. At two years, 30% of patients that had received OGX-011 with first-line chemotherapy were alive, comparing favorably to other previously reported studies in NSCLC.
  - The FDA granted OGX-011 Fast Track Designation for use in combination with docetaxel for progressive metastatic prostate cancer.
  - OncoGenex reached an agreement with the FDA on the design of a Phase 3 registration trial of OGX-011 in patients with castrate resistant prostate cancer, via the Special Protocol Assessment process.
- Lilly reported positive Phase 1 clinical trial results for LY2181308 that targets survivin for the treatment of cancer, and advanced LY2181308 into multiple Phase 2 trials.

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

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

Corporate Highlights

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

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

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

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

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

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

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Regulus Highlights

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

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

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Development Projects

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

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

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

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

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Pipeline

Cardiovascular Franchise

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

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

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

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

In Phase 2 studies, mipomersen, a weekly injectable therapeutic, was observed to reduce LDL-C beyond reductions achieved with standard lipid-lowering drugs, enabling more patients to achieve LDL-C targets. It was also observed to

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reduce triglycerides, lipoprotein (a), or Lp(a), and serum apoB, all generally accepted risk factors for cardiovascular disease. We believe that mipomersen may be of benefit for patients who cannot control their cholesterol with current therapies.

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

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

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

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

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

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

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

Cardiovascular research—We continue to build our cardiovascular disease franchise by evaluating potential drug targets that influence the onset and progression of cardiovascular disease. In addition, we intend to expand our cardiovascular franchise with additional drugs to treat various aspects of cardiovascular disease through complimentary

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

Metabolic Franchise

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

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

Scientists have long recognized PTP-1B as an attractive target for treatment of diabetes, but due to structural similarities among closely related proteins, pharmaceutical companies have had difficulty identifying small molecule drugs with sufficient specificity to be safe. Our antisense technology

allows us to design very specific drugs that inhibit PTP-1B and that do not inhibit other protein family members, making it possible to reduce PTP-1B activity without affecting other closely related proteins that would likely lead to unwanted side effects.

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

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

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

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

OMJP-GCCR —We licensed our glucocorticoid receptor, or GCCR, program to OMJP as part of a metabolic disease collaboration we established in 2007. Glucocorticoid hormones have a variety of effects throughout the body, including promoting liver glucose production and fat storage. Although scientists have long recognized the inhibition of GCCR as an attractive strategy for development of therapeutics for type 2 diabetes, the side effects associated with systemic GCCR inhibition have challenged developers of traditional drugs. Antisense inhibitors of GCCR take advantage of the unique tissue distribution of oligonucleotides that allows the antisense drugs to antagonize glucocortocoid action primarily in

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liver and fat tissue. Notably, antisense drugs do not reduce GCCR expression in the central nervous system or adrenal glands. Inhibiting GCCR expression in these two organs can lead to systemic side effects.

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

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

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

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

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

Cancer Portfolio

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

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

OncoGenex recently reported positive survival results from a Phase 2 study of OGX-011 in combination with docetaxel and prednisone compared to docetaxel and prednisone alone for first-line treatment of metastatic castrate resistant prostate cancer. The National Cancer Institute of Canada, Clinical Trials

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

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

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

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

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

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

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

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

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

Neurodegenerative

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

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toxicology studies. In addition, as part of our alliance with Genzyme, we have a preferred partner relationship for the development and commercialization of antisense drugs for neurodegenerative and certain rare diseases.

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

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

Other Drug Development Highlights

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

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

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

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

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

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

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

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

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

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

Antisense Technology

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

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

When a cell transcribes information from a DNA gene into messenger RNA or mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template and information stored in the DNA strand is copied into a complementary mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in so doing, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the synthesis of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the "sense" strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense"

strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Specifically, all of our antisense drugs in development cause a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target mRNA. The drug itself remains intact during this process, so it can remain active against additional target mRNA molecules and repeatly trigger their degradation. Our antisense drugs can selectively bind to a mRNA that codes for a specific protein and will not bind to closely related RNAs, providing a level of specificity that is better than traditional drugs. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique specificity means that antisense drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets.

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

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

Other Antisense Mechanisms

RNAi

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

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

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

Splicing

Splicing is a cellular mechanism through which a single gene can lead to the production of many different, albeit closely related, proteins. To be converted into proteins, genes must be initially copied into a pre-mRNA. Pre-mRNA often contains extra sequence information that must be removed prior to translation into the protein. Scientists call this process

splicing. Controlling pre-mRNA splicing can affect the production of proteins providing us with another way to control the production of disease-causing proteins. Using antisense technology, we have been able to control how these stretches of RNA are spliced back together. Our scientists in collaboration with Cold Spring Harbor recently published research that demonstrated the feasibility of using our antisense technology to control pre-mRNA splicing for the treatment of spinal muscular atrophy. This collaborative work demonstrates the diversity of our technology and the potential to utilize many different antisense approaches to treat disease.

New Antisense Targets

MicroRNAs

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

Other Oligonucleotide Opportunities

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

Regulus Therapeutics

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

Regulus Business

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

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

Regulus exclusively controls many of the early fundamental patent portfolios in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Our "Crooke" patent estate provides Regulus exclusive rights to RNA-based product compositions and methods of treatment in the field of microRNA-based therapeutics. Regulus has also

continued to build upon its intellectual property estate through the exclusive license of intellectual property relating to antagonizing a specific microRNA, miR-181a, to regulate immune responses. In total, Regulus' intellectual property portfolio includes early fundamental intellectual property in the field of microRNA, as well as over 900 filed patent applications pertaining to chemical modification of oligonucleotides for therapeutic applications, of which over 600 have been issued.

In April 2008, Regulus formed a strategic alliance with GlaxoSmithKline, or GSK to discover, develop and market microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The transaction included a $20 million upfront payment to Regulus and up to $144.5 million in potential development, regulatory and sales milestone payments by GSK for each of the four microRNA-targeted

therapeutics discovered as part of the collaboration. In total, the transaction has a potential value of nearly $600 million. Additionally, Regulus is eligible to receive royalties up to double digits on worldwide sales of products resulting from the collaboration.

Regulus Therapeutic Programs

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

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

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

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

Ibis Biosciences, Inc.

In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total acquisition price of $215 million. The Ibis technology is a product of our innovation and a tangible example of the value our technology provides outside of drug discovery and development. In late 2007, we began commercializing the Ibis T5000 instrument and research kits used with the Ibis T5000. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. Early this year AMI completed the acquisition of Ibis and we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis systems that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5% of net sales over $140 million through net sales of $2.1 billion and 3% of net sales over $2.1 billion, with the percentages subject to reduction in certain circumstances. As a result, we believe this is a very attractive transaction for our shareholders.

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Our partnership strategy has allowed us to build a clinical development pipeline of 19 drugs, to create a broad base of potential milestones, royalties, profit sharing and earn out payments and to control our drug development expenses. In this

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way, we remain a focused and efficient research and development organization that can continue to discover new drugs and expand ours and our partners' pipelines. In order to maximize the value of our antisense technology and our drug discovery platform, we pursue several different categories of partnerships, including traditional pharmaceutical alliances and licenses, drug discovery and development satellite companies and technology development satellite companies. Our partnership strategy allows us to minimize our risk in discovering antisense drugs in new and underserved disease areas.

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

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

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

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

Traditional Pharmaceutical Alliances and Licensing

We license our drugs to pharmaceutical partners for further development and commercialization and these partnerships benefit us, our drugs, and our partners. With the resources and experience of our pharmaceutical partners guiding drug development, our drugs should advance more rapidly and access

larger markets than if we developed them on our own. Our partnering activity coupled with our efficient drug discovery technology enables us to develop the majority of our drugs that are in our core therapeutic areas through early proof-of-concept ourselves prior to licensing.

Genzyme Corporation

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

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

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

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

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

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

Bristol-Myers Squibb Company

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

Pfizer Inc.

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

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly, which included a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases. Subsequently, we extended the research collaboration with Lilly to focus on a select number of targets. As part of the collaboration, Lilly licensed LY2181308, our antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. As of December 31, 2008, we had earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. Lilly is responsible for the preclinical and clinical development of LY2181308 and LY2275796. We will receive additional milestone payments aggregating up to $25 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and in addition, royalties on future product sales of these drugs.

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

Merck & Co., Inc.

In June 1998, we entered into a multi-year research collaboration and license agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a

drug discovered in this collaboration into Phase 1 clinical trials for which we received a $1 million milestone payment. In addition to the milestone payment we received, Merck will pay us

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aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales. We recently removed the Merck drug from our pipeline because we have been unable to verify the development status of the drug with Merck. During 2008 and 2007, we did not recognize any revenue from our relationship with Merck, compared to $1.1 million in 2006, which was made up of the $1 million milestone payment and $60,000 pursuant to a non-exclusive license agreement.

Drug Discovery and Development Satellite Company Collaborations

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

Achaogen, Inc.

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

Altair Therapeutics Inc.

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

Antisense Therapeutics Limited

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

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

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

Atlantic Pharmaceuticals Limited, formerly Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based company that gastrointestinal drug developers founded in 2006 to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Pharmaceuticals plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. At December 31, 2008 and 2007, we owned approximately 13% of Atlantic Pharmaceuticals' equity. In addition, assuming Atlantic Pharmaceuticals successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Pharmaceuticals meets specific development milestones, at Atlantic Pharmaceuticals' request, we will attempt to identify a second-generation lead drug candidate for Atlantic Pharmaceuticals. Atlantic

Pharmaceuticals may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Pharmaceuticals is solely responsible for the continued development of alicaforsen, and, if selected, the second-generation lead drug candidate. During 2008 and 2007, we did not recognize any revenue from our relationship with Atlantic Pharmaceuticals because we do not recognize revenue when we receive equity in private companies.

Excaliard Pharmaceuticals, Inc.

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

iCo Therapeutics Inc.

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

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

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

In November 2001, we established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug that targets clusterin. In July 2008, we amended and restated the original agreement with OncoGenex. Under the amended agreement, OncoGenex will independently develop and is responsible for all development costs and activities for OGX-011 and we will receive royalties for OGX-011 ranging from 5.5% to 7% of net sales. In addition, OncoGenex will pay us 30% of the upfront fees and milestone payments that

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OncoGenex receives if OncoGenex licenses OGX-011 prior to initiation of registration trials, 25% if OncoGenex licenses OGX-011 before 20% of patients have been enrolled in a registration trial, 20% if OncoGenex licenses OGX-011 prior to marketing approval and 15% thereafter. In August 2003, the companies entered into a collaboration and license agreement for the development partnership to include the development of the second-generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. OncoGenex issued to us $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and royalties on product sales. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-225.

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

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

Novosom AG

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

Technology Development Satellite Company Collaborations

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

Archemix Corp.

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

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Alnylam Pharmaceuticals, Inc.

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

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

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

Ercole Biotech, Inc.

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

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

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

External Project Funding

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

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CHDI, Inc.

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

Korea Institute of Toxicology

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

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

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

Intellectual Property Sale and Licensing Agreements

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

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

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

Integrated DNA Technologies, Inc.

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

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functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees and will pay royalties on sales of the drugs utilizing the technology IDT licensed to us.

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

Abbott Molecular Inc.

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

- In 2008, AMI invested $40 million in Ibis providing the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics; and
- We granted AMI an exclusive call option to acquire from us all remaining Ibis capital stock.

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

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

Eyetech Pharmaceuticals, Inc.

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

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

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

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for

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initial and ongoing payments from Roche Molecular Systems to us. During 2008, 2007 and 2006, we recognized revenue of $1.2 million, $807,000 and $200,000, respectively, from our relationship with Roche Molecular Systems.

Regulus Collaborations

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

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

GlaxoSmithKline

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

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

Manufacturing

Drug Discovery and Development

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide drugs, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide drugs. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the drugs. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions. Due to the growing numbers of our antisense drug development partners and the clinical successes of our antisense drugs, including mipomersen, we anticipate that we will need to increase our manufacturing capacity. In order to accommodate our increasing demand, we are currently upgrading and optimizing the efficiency of our manufacturing facility. We started this process in 2008 and expect to complete the upgrades in 2009.

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

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

Regulus Therapeutics

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

Patents and Proprietary Rights

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

Isis Pharmaceuticals, Inc.

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

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

Other Isis patents claim oligonucleotides comprising specific antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that make oligonucleotides comprising them particularly suited for a particular cellular mechanism of action. For example, US Patent No. 7,015,315, the '315 patent, claims oligonucleotides comprising a region modified with 2'-O-alkyl substituents, such as 2'-MOE, and a region comprising deoxyribonucleosides. Oligonucleotides incorporating these motifs, sometimes referred to as chimeric compounds or gapmers are designed to exploit the RNase H mechanism. All of our development compounds, including mipomersen, contain this gapmer antisense drug design motif. In fact, the '315 patent covers each of our second generation development candidate antisense compounds until March of 2023. Similarly, US Patent Nos. 5,898,031, 6,107,094, 7,432,249 and 7,432,250 (the Crooke Patents), cover oligonucleotides comprising methods and motifs useful for exploiting the RNAi

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pathway until June of 2016. We licensed the Crooke Patents to Alnylam for the development of double-stranded therapeutics and to Regulus for the development of microRNA-based therapeutics.

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

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

Regulus Therapeutics

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

Government Regulation

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

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

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

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Competition

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

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

Employees

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

Executive Officers of Isis

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

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

Richard S. Geary, Ph.D	51	Senior Vice President, Development

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

Chairman, Chief Executive Officer and President

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

B. LYNNE PARSHALL, J.D.

Director, Chief Operating Officer, Chief Financial Officer and Secretary

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

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C. FRANK BENNETT, Ph.D.

Senior Vice President, Antisense Research

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

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

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

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this Annual Report on Form 10-K and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Associated with our Businesses as a Whole

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

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

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

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

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Altair, ATL, Atlantic Pharmaceuticals, BMS, iCo, Lilly, Merck, OncoGenex, OMJP and Teva. In addition, in January 2008 we entered a major strategic alliance with Genzyme in

which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;

- environmental damage resulting in costly clean up; and

- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

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

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

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

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

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

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

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

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^{5}/_{8}$% convertible subordinated notes, including the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

The continuing deterioration in the global credit markets, the financial services industry and the U.S. capital markets, the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the current economic crisis is uncertain. It is possible that the current crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers

and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

Risks Associated with our Drug Discovery and Development Business

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

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drugs, including mipomersen and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product,

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including mipomersen and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

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

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

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

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

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

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

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

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

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

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, even if approved for commercialization, doctors may not

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use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

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

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Item 3. Legal Proceedings

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

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

Not applicable.

PART II

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

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

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

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

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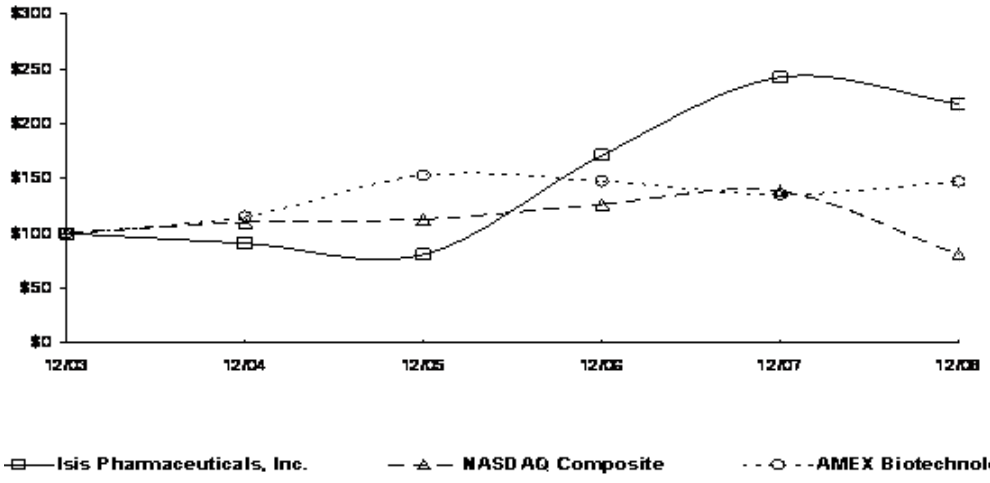
Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2003 in our common stock, the NASDAQ Composite Index (total return) and the AMEX Biotech Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



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

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

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

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

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

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

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

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

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

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

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. Our highly efficient and prolific drug discovery platform enables us to expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover

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

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

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

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

Business Segments

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

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

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

Ibis Biosciences, Inc. In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total purchase price of $215 million. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in

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expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. Early in 2009, AMI completed the acquisition of Ibis and we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis products that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5% of net

sales over $140 million through net sales of $2.1 billion and 3% of net sales over $2.1 billion, with the percentages subject to reduction in certain circumstances.

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

Critical Accounting Policies

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

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

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in available-for-sale securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

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

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

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

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

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

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

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

Valuation of Investments in Marketable Securities

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

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

Valuation of Long-Lived Assets

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

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

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

Valuation of Inventory

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

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we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

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

Segment Information

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

Stock-Based Compensation

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

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

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

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

We record stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, at their fair value in accordance with the requirements of SFAS 123R, then periodically remeasure them in accordance with EITF 96-18, *Accounting for Equity*

Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services, and recognize them over the service period.

Results of Operations

Years Ended December 31, 2008 and December 31, 2007

Revenue

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

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

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

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

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

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Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

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

Licensing and Royalty Revenue

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

Regulus Therapeutics

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

Operating Expenses

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

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

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

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

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

Research and Development Expenses

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

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

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

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

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

Drug Discovery & Development

Antisense Drug Discovery

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

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

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

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

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

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Antisense Drug Development

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

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

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

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

Manufacturing and Operations

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

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

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

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

R&D Support

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

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

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

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

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of business development, legal, human resources, investor relations, finance and Regulus' general and administrative expenses, which began in September 2007 when we and Alnylam formed Regulus. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above. Until our acquisition of Symphony GenIsis in September 2007, general and administrative expenses also included Symphony GenIsis' general and administrative expenses.

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

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

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

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

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

Regulus Therapeutics

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

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

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $7.6 million for the year ended December 31, 2008 compared to $612,000 in 2007. Regulus began its operations in September 2007, therefore its 2007 operating expenses only reflect four

months of activity compared to the entire year in 2008. Also contributing to the increase in its operating expenses from 2007 to 2008 was the research and development activities associated with its strategic alliance with GSK, which began in April 2008. With the strategic alliance with GSK, it is anticipated that Regulus' expenses will increase over its run rate in 2008 as Regulus advances its research and development activities.

Investment Income

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

Interest Expense

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

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

Gain (Loss) on Investments, net

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

Loss on Early Retirement of Debt

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

Net Loss from Continuing Operations

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

Net Loss from Discontinued Operations

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

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

Net Loss Applicable to Common Stock

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

Net Loss per Share Applicable to Common Stock

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

Net Operating Loss Carryforward

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

Years Ended December 31, 2007 and December 31, 2006

Revenue

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

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

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

Licensing and Royalty Revenue

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

Operating Expenses

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

Our operating expenses were as follows (in thousands):

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

Research and Development Expenses

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

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

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

Drug Discovery & Development

Antisense Drug Discovery

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

Antisense Drug Development

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

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

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

Manufacturing and Operations

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

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R&D Support

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

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

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

General and Administrative Expenses

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

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

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

Restructuring Activities

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

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

Investment Income

Investment income for the year ended December 31, 2007 totaled $11.4 million, compared to $6.0 million for 2006. The increase in investment income was primarily due to a higher average cash balance in 2007 compared to 2006 as a result of the proceeds we received from the issuance of our 2 5/8% convertible subordinated notes, the $15 million upfront licensing fee received from BMS, the $26.5 million sublicensing fee received from Alnylam, the $10 million invested in Regulus, the $52 million upfront licensing fee, milestone payment and initial research and development funding received from our collaboration with OMJP and the $10.3 million from stock options exercised in 2007, offset by the repayment of our 5 1/2% notes and the $80.4 million payment for the acquisition of Symphony GenIsis.

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Interest Expense

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

Gain on Investments, net

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

Loss on Early Retirement of Debt

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

Net Loss from Continuing Operations

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

Net Loss from Discontinued Operations

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

Net Loss Applicable to Common Stock

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

Net Loss per Share

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

Net Operating Loss Carryforward

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

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

Liquidity and Capital Resources

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

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

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

The following table summarizes our contractual obligations as of December 31, 2008. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2 5/8% Convertible Subordinated Notes	$ 162.5	$ —	$ —	$ —	$ 162.5
GSK Convertible Promissory Note, including accrued interest	$ 5.2	$ —	$ 5.2	$ —	$ —
Equipment Financing Arrangement	$ 6.5	$ 2.1	$ 4.4	$ —	$ —
Other Obligations	$ 0.3	$ —	$ —	$ —	$ 0.3
Operating Leases	$ 17.7	$ 3.1	$ 4.5	$ 2.3	$ 7.8

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

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

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. The $162.5 million convertible subordinated notes bear interest at 2 5/8%, which is payable semi-annually, and mature in 2027. The 2 5/8% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem

these notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2 5/8% notes are also able to require us to repurchase the 2 5/8% notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2 5/8% notes being repurchased plus accrued interest and unpaid interest. Using the net proceeds from the issuance of our 2 5/8% notes, in 2007, we repaid the entire $125 million of our 5 1/2% convertible subordinated notes due 2009.

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

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

held for sale line item within the accompanying Consolidated Balance Sheet. We expect to draw down the remaining unused portion of this loan agreement in the first quarter of 2009.

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

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

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

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

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

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Item 8. Financial Statements and Supplementary Data

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

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

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

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

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

Changes in Internal Control over Financial Reporting

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

Management's Report on Internal Control over Financial Reporting

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

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

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

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

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

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

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

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

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

In our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2008, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2008 and 2007, and the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2008 of Isis Pharmaceuticals, Inc. and our report dated February 23, 2009, expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
February 23, 2009

Item 9B. Other Information

Not applicable

PART III

Item 10. Directors, Executive Officers and Corporate Governance

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

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

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

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Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance Under Equity Compensation Plans

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

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	6,165,000	$ 9.16	4,084,000(c)
Equity compensation plans not approved by stockholders(b)	3,151,000	$ 13.09	277,000
Total	9,316,000	$ 10.49	4,361,000

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

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

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

Description of 2000 Broad-Based Equity Incentive Plan

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

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

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the option holder's employment or service as a consultant, employee or director. Options granted pursuant to the April 2003 stock option exchange program as discussed in the Notes to the Consolidated Financial Statements, expired on December 31, 2008. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating

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dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

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

In the event of:

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

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000

Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

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

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

Item 14. Principal Accountant Fees and Services

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

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 63.

(b) Exhibits

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

(c) Financial Statement Schedules

None.

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SIGNATURES

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

ISIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 26, 2009
/s/ B. LYNNE PARSHALL Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	February 26, 2009
/s/ SPENCER R. BERTHELSEN	Director	February 26, 2009

Spencer R. Berthelsen, M.D.		
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	February 26, 2009
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	February 26, 2009
/s/ FREDERICK T. MUTO Frederick T. Muto	Director	February 26, 2009
/s/ JOHN C. REED, M.D. PH.D. John C. Reed, M.D., Ph.D.	Director	February 26, 2009
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 26, 2009

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INDEX TO EXHIBITS

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

10.12	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008 (with certain confidential information deleted).(8)
10.13	License Agreement between the Registrant and Atlantic Healthcare (UK) Limited dated March 7, 2007 (with certain confidential information deleted).(5)
10.14	VLA4 Partner Support Agreement between the Registrant and Teva Pharmaceutical Industries Ltd dated February 8, 2008 (with certain confidential information deleted).(8)
10.14	Amended and Restated License Agreement dated July 2, 2008 between the Registrant and OncoGenex Technologies Inc. (with certain confidential information deleted) (22)
10.16	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)

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10.17	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.18	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.19	Registrant’s Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(23)
10.20*	Registrant’s Amended and Restated 2002 Non-Employee Directors’ Stock Option Plan.(13)
10.21*	Registrant’s Form of 2002 Non-Employee Directors’ Stock Option Agreement.(29)
10.22	Product Development and Commercialization Agreement between Regulus Therapeutics LLC and Glaxo Group Limited dated April 17, 2008 (with certain confidential information deleted). (12)
10.23*	Amendment No. 1 to Isis Pharmaceuticals, Inc. Employee Stock Purchase Plan.(28)
10.24*	Amended and Restated Severance Agreement dated December 3, 2008 between Isis and Stanley T. Crooke. (21)
10.25*	Amended and Restated Severance Agreement dated December 3, 2008 between Isis and B. Lynne Parshall. (21)
10.26	Strategic Collaboration and License Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(18)
10.27	Amendment No. 1 to Sale Agreement dated October 14, 2007 between Isis and DRT 3.(15)
10.28	Loan Agreement dated October 15, 2008 between the Registrant and RBS Asset Finance, Inc.
10.29	Amendment No. 1 to License Agreement between the Registrant and Eyetech.(16)
10.30	Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(16)
10.31	Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(16)
10.32*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(16)
10.33*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(16)
10.34*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director’s Stock Option Plan.(16)
10.35*	Employment Agreement dated December 29. 2008 between Regulus Therapeutics and Kleanthis G. Xanthopoulos, PhD
10.36	Amendment No.1 to Rights Agreement dated April 7, 2005.(27)
10.37	Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted). (26)
10.38	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(23)
10.39	Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(23)
10.40	Pre-Clinical Development Collaboration Agreement dated March 23, 2007 between the Registrant and Korean Institute of Toxicology (with certain confidential information deleted).

10.41	Stock Purchase Agreement dated December 17, 2008, among the Registrant, Ibis Biosciences, Inc. and Abbott Molecular Inc. (with certain confidential information deleted).
10.42	Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(14)
10.43	Collaboration and License Agreement between the Registrant and Bristol-Myers Squibb Company dated May 8, 2007 (with certain confidential information deleted). (7)
10.44	Research Agreement dated October 22, 2007 between the Registrant and CHDI, Inc. (with certain confidential information deleted).(4)

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10.45	Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007 (with certain confidential information deleted).(20)
10.46	License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).(20)
14.1	Registrant's Code of Ethics and Business Conduct.(21)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney.(30)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)

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

(2) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2008 Annual Meeting of Stockholders, filed with the SEC on April 18, 2008, and incorporated herein by reference.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2008 and 2007, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2008. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc at December 31, 2008 and 2007, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2008, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the effectiveness of Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2008, based on criteria established in Internal Control- Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 23, 2009 expressed an unqualified opinion thereon.

/s/ ERNST AND YOUNG

San Diego, California
February 23, 2009

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

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

See accompanying notes.

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

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

See accompanying notes.

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

Description	Common stock Shares	Common stock Amount	Additional paid in capital	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2005	72,201	$ 72	$ 770,263	$ 3,178	$ (770,848)	$ 2,665
Comprehensive Loss:						
Net loss applicable to common stock	—	—	—	—	(45,903)	(45,903)
Change in unrealized gains	—	—	—	1,100	—	1,100
Comprehensive loss	—	—	—	—	—	(44,803)
Options exercised and employee stock purchase plan	1,883	2	11,518	—	—	11,520
Warrants exercised	229	—	—	—	—	—
Share-based compensation expense	—	—	5,747	—	—	5,747
Issuance of common stock under Azimuth equity financing	7,971	8	74,836	—	—	74,844
Issuance of warrants to Symphony Capital	—	—	18,590	—	—	18,590
Balance at December 31, 2006	82,284	$ 82	$ 880,954	$ 4,278	$ (816,751)	$ 68,563
Comprehensive Loss:						
Net loss	—	—	—	—	(10,994)	(10,994)
Change in unrealized losses	—	—	—	(3,740)	—	(3,740)
Comprehensive loss	—	—	—	—	—	(14,734)
Options exercised and employee stock purchase plan	1,510	2	11,349	—	—	11,351
Warrants exercised	61	—	—	—	—	—
Share-based compensation expense	—	—	9,910	—	—	9,910
Excess purchase price over carrying value of	—	—	(125,311)	—	—	(125,311)

noncontrolling interest in Symphony GenIsis, Inc.						
Issuance of common stock for Symphony GenIsis acquisition	3,384	3	51,090	—	—	51,093
Balance at December 31, 2007	87,239	$ 87	$ 827,992	$ 538	$ (827,745)	$ 872
Comprehensive Loss:						
Net loss applicable to common stock	—	—	—	—	(11,963)	(11,963)
Change in unrealized gains	—	—	—	444	—	444
Comprehensive loss	—	—	—	—	—	(11,519)
Options exercised and employee stock purchase plan	1,510	2	12,550	—	—	12,552
Warrants exercised	3,423	3	160	—	—	163
Share-based compensation expense	—	—	15,063	—	—	15,063
Issuance of common stock to Genzyme Corporation	5,000	5	49,956	—	—	49,961
Balance at December 31, 2008	97,172	$ 97	$ 905,721	$ 982	$ (839,708)	$ 67,092

See accompanying notes.

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

	Years Ended December 31,		
	2008	2007	2006
Operating activities:			
Net loss	$ (11,963)	$ (10,994)	$ (45,903)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	2,868	2,667	3,854
Amortization of patents	1,610	1,623	1,633
Amortization of licenses	2,339	2,335	2,335
Amortization of discount on investments, net	(225)	(773)	(606)
Amortization of debt issuance costs	797	913	603
Share-based compensation expense	15,063	9,910	5,747
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	(23,157)	(23,021)
Loss attributed to noncontrolling interest in Regulus Therapeutics Inc.	(4,734)	(629)	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	(2,103)	—	—
Gain from derivative instruments issued to Abbott Molecular Inc.	(5,326)	—	—
(Gain) loss on investments, net	965	(3,510)	(2,263)
Loss on early retirement of debt	—	3,212	—
Non-cash losses related to patents and property, plant and equipment	1,877	896	2,410
Changes in operating assets and liabilities:			
Contracts receivable	1,238	(3,782)	1,523
Inventory	(1,323)	(1,956)	90
Other current and long-term assets	(2,657)	(494)	(796)
Accounts payable	962	(794)	1,214
Accrued compensation	(3,255)	4,239	2,516
Accrued liabilities	4,923	723	(2,135)
Deferred contract revenues	210,975	55,665	(426)
Net cash provided by (used in) operating activities	212,031	36,094	(53,225)
Investing activities:			
Purchase of short-term investments	(483,129)	(95,371)	(107,025)
Proceeds from the sale of short-term investments	265,951	119,956	72,575
Purchases of property, plant and equipment	(13,665)	(2,293)	(1,042)
Acquisition of licenses and other assets	(3,402)	(2,717)	(1,514)
Proceeds from the sale of strategic investments	—	5,181	4,397
Acquisition of Symphony GenIsis, Inc.	—	(80,400)	—
Net cash used in investing activities	(234,245)	(55,644)	(32,609)
Financing activities:			
Net proceeds from issuance of equity	12,714	11,351	86,364
Proceeds from issuance of convertible promissory note to GlaxoSmithKline	5,000	—	—
Proceeds from equipment financing arrangement	7,048	—	—
Proceeds from issuance of $2^5/_8$% convertible subordinated notes, net of issuance costs	—	157,056	—
Principal and redemption premium payment on prepayment of the $5^1/_2$% convertible subordinated notes	—	(127,021)	—
Principal payments on debt and capital lease obligations	(7,239)	(7,736)	(7,851)
Proceeds from stock purchase by Genzyme Corporation, net of fees	49,962	—	—
Proceeds from capital contributions to Ibis Biosciences, Inc.	40,000	—	—
Proceeds from capital contribution to Regulus Therapeutics Inc.	100	10,000	—

Proceeds from contribution to noncontrolling interest in Symphony GenIsis, Inc., net of fees	—	—	70,950
Net cash provided by financing activities	107,585	43,650	149,463
Net increase in cash and cash equivalents	85,371	24,100	63,629
Cash and cash equivalents at beginning of year	138,614	114,514	50,885
Cash and cash equivalents (including cash and cash equivalents classified as assets held for sale of $6.1 million, $0 and $0 at December 31, 2008, 2007 and 2006, respectively) at end of year	$ 223,985	$ 138,614	$ 114,514
Supplemental disclosures of cash flow information:			
Interest paid	$ 4,607	$ 6,212	$ 8,431
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ —	$ —	$ 18,590
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 2,873	$ 1,013	$ 979
Common stock issued for Symphony GenIsis, Inc. acquisition	$ —	$ 51,093	$ —
Acquisition of property, plant and equipment	$ —	$ —	$ 361

See accompanying notes

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ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Significant Accounting Policies

Basis of Presentation

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

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

Organization and business activity

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

Basic net loss per share

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

Contract revenue and expenses

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

Revenue Recognition

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

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

Research and development revenue under collaborative agreements

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

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

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

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

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

Licensing and royalty revenue

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

Concentration of credit risk

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

Cash, cash equivalents and short-term investments

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

We also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting according to Accounting Principles Board ("APB") 18, *The Equity Method of Accounting for Investments in Common Stock*. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During 2008, we recognized a $965,000 loss on investments consisting of $1.2 million non-cash loss related to the other-than-temporary impairment of our equity investment in OncoGenex Technologies Inc., a subsidiary of OncoGenex Pharmaceuticals

Inc. and a $198,000 gain that we realized on our available-for-sale securities. See further discussion about our investment in OncoGenex in *Note 7—Collaborative Arrangements and Licensing Agreements*. During 2007, we sold the remainder of our equity securities of Alnylam Pharmaceuticals, Inc. that we owned resulting in a realized gain of $3.5 million, compared to a net gain on investments of $2.3 million during 2006. The net gain on investments during 2006 represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we owned, offset by a non-cash loss of $465,000 related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Limited, or ATL. We determined that there were no other-than-temporary declines in value of investments in 2007.

Inventory valuation

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

Property, plant and equipment

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

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

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

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

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

Licenses

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

Patents

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

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

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

2013	$	0.7

Fair value of financial instruments

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

Long-lived assets

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

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Use of estimates

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

Consolidation of variable interest entities

We have implemented the provisions of FIN 46R, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of December 31, 2008, we had collaborative arrangements with nine entities that we considered to be variable interest entities ("VIE") under FIN 46R. For 2008, our consolidated financial statements include two variable interest entities, Ibis and Regulus, for which we were the primary beneficiary. For 2007, our consolidated financial statements included three variable interest entities, Ibis, Regulus and Symphony GenIsis, for which we were the primary beneficiary. For 2006, our consolidated financial statements included two variable interest entities, Ibis and Symphony GenIsis, for which we were the primary beneficiary. Until our acquisition of Symphony GenIsis in September 2007, we identified Symphony GenIsis as a variable interest entity that we consolidated.

Stock-based compensation

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

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

As permitted by SFAS 123R, we utilize the Black-Scholes model as our method of valuation for stock-based awards granted. On the grant date, we use our stock price as well as assumptions regarding a number of highly complex and subjective variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although the estimated fair value of employee stock options is determined in accordance with SFAS 123R using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

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

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

Comprehensive loss

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

Segment information

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

Fair Value Measurements

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

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

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

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

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

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

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

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

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

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

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

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

Income Taxes

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

Impact of recently issued accounting standards

In December 2007, the FASB issued SFAS 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment to ARB No. 51*. This statement recharacterizes the accounting and reporting for minority interests as noncontrolling interests and classifies them as a component of equity. SFAS 160 applies to all entities that prepare consolidated financial statements, but will affect only those entities that have an outstanding noncontrolling interest in one or more subsidiaries or that deconsolidate a subsidiary. This statement is effective for fiscal years beginning after December 15,

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2008, and will be effective for our fiscal year 2009. We do not expect the adoption of SFAS 160 to have a material impact on our results of operations and financial position but the requirements of SFAS 160 will impact how we present noncontrolling interests in our consolidated financial statements. SFAS 160 requires that we apply the standard retrospectively to all periods we present.

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

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

2. Discontinued Operations

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

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

	Year Ended December 31,		
	2008	2007	2006
Revenue	$ 12,586	$ 11,277	$ 9,673
Total operating expenses	28,393	17,306	12,573
Loss from operations	(15,807)	(6,029)	(2,900)

Other income, net	5,317	—	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	2,103	—	—
Net loss from discontinued operations	$ (8,387)	$ (6,029)	$ (2,900)
Basic and diluted net loss per share from discontinued operations	$ (0.09)	$ (0.07)	$ (0.04)

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

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

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

3. Investments

As of December 31, 2008, our excess cash is primarily invested in commercial paper and debt instruments of financial institutions, corporations and U.S. government agencies with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2008:

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

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

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

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

Subtotal	$ 3,005	$ 604	$ —	$ (1,163)	$ 2,446
	$ 275,707	$ 1,697	$ (715)	$ (1,163)	$ 275,526

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

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

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

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We intend to hold these securities to maturity and anticipate full recovery of amortized cost with respect to these securities at maturity.

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4. Long-Term Obligations and Commitments

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

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

Standard Operating Debt

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

GlaxoSmithKline Convertible Promissory Note

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

Convertible Subordinated Notes

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2 5/8%, which is payable semi-annually. The 2 5/8% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. At December 31, 2008, the principal and accrued interest outstanding on the notes was $162.5 million and $1.6 million, respectively, and the fair value was $162.3 million. We

did not include the effect of the conversion of these convertible notes into our common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

We will be able to redeem the 2⅝% 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 2⅝% 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 2⅝% notes being repurchased plus accrued and unpaid interest.

In 2007, we used the net proceeds from the issuance of the 2⅝% notes to repurchase our 5½% 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.

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Equipment Financing Arrangement

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

Other Obligations

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

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

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

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

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

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

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

5. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2008 and 2007, there were no shares of Isis' Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible

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Exchangeable 5% Preferred Stock outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series C Junior Participating Preferred Stock

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

Common Stock

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

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

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

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

Stock Option Plans

1989 Stock Option Plan

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

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which, as amended, provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange

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program expired on December 31, 2008. At December 31, 2008, a total of 3,151,217 options were outstanding, 1,199,591 shares were exercisable, and 277,029 shares were available for future grant under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

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

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

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

2002 Non-Employee Directors' Stock Option Plan

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

Employee Stock Purchase Plan

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

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Stock Option Activity and Stock-Based Compensation Expense

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

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

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

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

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

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

Impact of the Adoption of SFAS 123R

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

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

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

Determining Fair Value

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

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

Employee Stock Options:

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

Board of Director Stock Options:

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

ESPP:

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

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

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

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

Expected Life. The expected term of stock options granted represents the period of time that we expect them to be outstanding. For the 2002 Plan, we estimated the expected term of options granted based on historical exercise patterns. For the 1989 Plan and 2000 Plan, we estimated the expected term of options granted subsequent to January 1, 2008, based on

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historical exercise patterns. The expected term for stock options granted prior to January 1, 2008 was a derived output of the simplified method, as allowed under SAB 107.

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

Warrants

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

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

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

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

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

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

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

6. Income Taxes

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

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

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

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

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

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

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

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

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Genzyme Corporation

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing of mipomersen and a

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

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

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

from Genzyme, which represented 45% of our total revenue for 2008. Our Consolidated Balance Sheet at December 31, 2008 included deferred revenue of $226.8 million, which represents the remaining premium and licensing fee.

Ortho-McNeil-Janssen Pharmaceuticals, Inc.

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

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

Bristol-Myers Squibb Company

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

sales of products resulting from the collaboration. During 2008 and 2007, we recognized revenue of $12.0 million and $5.2 million related to the upfront licensing fee, milestone payment and the research funding, which represented 11% and 9% of our total revenue for those years. Our balance sheets at December 31, 2008 and 2007 included deferred revenue of $6.7 million and $11.7 million, respectively, related to the upfront licensing fee.

Pfizer Inc.

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

Eli Lilly and Company

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

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

Merck & Co., Inc.

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

Drug Discovery and Development Satellite Company Collaborations

Achaogen, Inc.

In January 2006, we licensed our proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and that clinicians use to treat serious bacterial infections. In exchange for the exclusive, worldwide license to our aminoglycoside program, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. At the time of receipt, we recognized a valuation allowance of $1.5 million to offset this asset as realization of this asset is uncertain. At December 31, 2008 and 2007, we owned less than 10% of Achaogen's equity. In early 2009, we received a $1 million milestone payment from Achaogen, consisting of $500,000 in cash and $500,000 in Achaogen securities, as a result of the filing of an IND for Achaogen's aminoglycoside drug, ACHN-490. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $33.5 million for the achievement of key clinical, regulatory and sales milestones. We will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the

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aminoglycoside program and products. During 2006, 2007 and 2008, we did not recognize any revenue from our relationship with Achaogen because we do not recognize revenue when we receive equity in private companies.

Altair Therapeutics Inc.

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

Antisense Therapeutics Limited

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

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

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

Atlantic Pharmaceuticals Limited

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

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Excaliard Pharmaceuticals, Inc.

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

iCo Therapeutics Inc.

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

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

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

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

In January 2005, we entered into a further agreement with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for all development costs and activities, and we have no further performance obligations. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427, which targets Hsp27. OncoGenex paid us an upfront fee of $750,000 with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will

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pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of December 31, 2008, OncoGenex had not triggered any of the milestone payments related to OGX-427.

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

Novosom AG

In August 2008, we granted Novosom an exclusive, worldwide license to access certain antisense inhibitors targeting CD40 mRNA for a number of indications. Novosom plans to target CD40, a well established target for both inflammatory diseases and autoimmune diseases, for indications such as Crohn's disease, organ transplant or rheumatoid arthritis. In exchange for the exclusive, worldwide license, Novosom paid us an upfront payment. In addition, assuming Novosom successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $6 million for the achievement of key clinical and regulatory milestones. We will also receive royalties on sales of these antisense drugs Novosom develops. Furthermore, if Novosom sublicenses an antisense drug using our technology, we may be entitled to a portion of the consideration Novosom

receives. We have no significant remaining obligations to perform under this agreement. During 2008, we recognized $375,000 in revenue from our relationship with Novosom

Technology Development Satellite Company Collaborations

Archemix Corp.

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

Alnylam Pharmaceuticals, Inc.

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

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay upon the occurrence of specified development and regulatory events. As of December 31, 2008, we did not have an RNAi-based drug in clinical development. Our Alnylam alliance

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provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery. As of December 31, 2008, we have earned a total of $36.1 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners.

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

Ercole Biotech, Inc.

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

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

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

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

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

External Project Funding

CHDI, Inc.

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

Symphony GenIsis, Inc.

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

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

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

Korea Institute of Toxicology

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

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

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

Intellectual Property Sale and Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

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

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Integrated DNA Technologies, Inc.

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

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

Abbott Molecular Inc.

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

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

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

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

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

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

Eyetech Pharmaceuticals, Inc.

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

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

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

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche Molecular Systems, a business unit of Roche Diagnostics, for use in the production of Roche Molecular Systems' diagnostic products. The royalty-bearing license grants Roche Molecular Systems non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche Molecular Systems to us. Our Consolidated Balance Sheets at December 31, 2008 and 2007 included deferred revenue of $200,000 related to our agreements with Roche Molecular Systems. During 2008, 2007 and 2006, we recognized revenue of $1.2 million, $807,000 and $200,000, respectively, from our relationship with Roche Molecular Systems.

Regulus Collaborations

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

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

GlaxoSmithKline

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

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

Regulus is amortizing the $15 million option fee into revenue over Regulus' six year period of performance. We show the $5 million note as a liability on our Consolidated Balance Sheet. For 2008, Regulus recognized revenue of $1.9

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million related to Regulus' collaboration with GSK. Our balance sheet at December 31, 2008 included deferred revenue of $13.1 million related to Regulus' collaboration with GSK.

8. Segment Information and Concentration of Business Risk

Segment Information

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

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

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

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

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

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

Year ended December 31, 2006	Drug Discovery and Development	Corporate	Total
Revenue:			

Research and development	$ 5,418	$ —	$ 5,418
Licensing and royalty	9,441	—	9,441
Total segment revenue	$ 14,859	$ —	$ 14,859
Income (loss) from operations	$ (65,754)	$ 536	$ (65,218)

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

Concentrations of Business Risk

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

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

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

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9. Restructuring Activities

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

10. Employee Post Employment Benefits

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

11. Legal Proceedings

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

12. Quarterly Financial Data (Unaudited)

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

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

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	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2007 Quarters				
Revenue(1)	$ 874	$ 1,922	$ 33,993	$ 21,555

Operating expenses(1)	19,831	19,802	23,820	27,810
Income (loss) from operations(1)	(18,957)	(17,880)	10,173	(6,255)
Net loss applicable to common stock(3)	$ (13,020)	$ (11,024)	$ (105,304)	$ (6,957)
Basic and diluted net loss per share(2)(3)	$ (0.16)	$ (0.13)	$ (1.25)	$ (0.08)

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

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

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

RBS Asset Finance

LOAN AGREEMENT

THIS LOAN AGREEMENT dated as of October 15, 2008 between **ISIS PHARMACEUTICALS, INC.**, a Delaware Corporation (together with its successors and permitted assigns, "Borrower"), and **RBS ASSET FINANCE, INC.**, a New York corporation (together with its successors and assigns, "Lender").

R ECITALS:

WHEREAS, Borrower desires to obtain one or more Loans from Lender in an aggregate principal amount not to exceed the Maximum Principal Amount, which Loans are to be secured by the Collateral;

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, and in consideration of the premises contained in this Agreement, Lender and Borrower agree as follows:

ARTICLE I: DEFINITIONS AND ACCOUNTING TERMS

Section 1.01. Defined Terms. The following terms shall have the following meanings for all purposes of this Loan Agreement:

"*Agreement*" means this Loan Agreement, as amended, supplemented, restated or otherwise modified from time to time in accordance with the terms hereof.

"*Borrower's State*" has the meaning ascribed to such term in Schedule I hereto.

"*Business Day*" means any day on which Lender is open for business and is neither a Saturday or Sunday nor a legal holiday on which banks are authorized or required to be closed in Chicago, Illinois.

"*Change of Control*" means a change in control of Borrower or any Guarantor, including, without limitation, a change in control resulting from direct or indirect transfers of voting stock or partnership, membership or other ownership interests, whether in one or a series of transactions. "Control" means the possession, directly or indirectly, of the power to direct or cause the direction of the management and policies of Borrower or any Guarantor, and a Change of Control shall occur if any Person or group (as such term is used in Section 13(d)(3) of the Exchange Act) acquires, after the date of this Agreement, the beneficial ownership directly or indirectly, of 50% or more of the voting power of the total outstanding stock or other ownership interests of Borrower or any Guarantor.

"*Closing Date*" means with respect to each Loan, the date that the proceeds of such Loan are disbursed to, or on behalf of, Borrower.

"*Closing Fee*" has the meaning ascribed to such term in Schedule I hereto.

"*Collateral*" means the property described on each Collateral Schedule, which property shall be acceptable to Lender, in its sole discretion, and any other assets of Borrower, any Guarantor or any other Person that are subject to a Lien in favor of Lender pursuant to any Loan Document.

"*Collateral Schedule*" means each schedule describing Collateral attached to and referencing a Note or Notes and executed by Borrower and Lender.

"*Commitment*" means Lender's obligation to make Loans to Borrower pursuant to Section 2.01 in an amount not to exceed the Maximum Principal Amount.

"*Commitment Termination Date*" means the earliest of (a) the date on which the aggregate Original Principal Amount of all Loans equals the Maximum Principal Amount, (b) the Scheduled Commitment Termination Date, (c) the date that an Event of Default described in subsection (i) of Section 7.01 occurs or (d) the date on which Lender elects to terminate the Commitment following (i) an Event of Default or (ii) the occurrence of a material adverse change in the business, assets or financial condition or prospects of Borrower or any Guarantor.

"*Default*" means any Event of Default or any condition, occurrence or event that, after notice or lapse of time or both, would constitute an Event of Default.

"*Default Rate*" has the meaning ascribed to such term in Section 2.05(c).

"*Environmental Laws*" means all federal, state, local, or foreign law (including any common law, consent decrees and administrative orders), statute, regulation, or ordinance (in each case, as amended from time to time) regulating, permitting,

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prohibiting or otherwise restricting the placement, discharge, release, generation, treatment or disposal upon or into any environmental media of any substance, pollutant, contaminant or waste that is now or hereafter classified or considered to be hazardous or toxic.

"*Event of Default*" has the meaning assigned to such term in Section 7.01.

"*Exchange Act*" means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

"*Financial Statements*" has the meaning ascribed to such term in Schedule I hereto.

"*Fixed Rate*" has the meaning ascribed to such term in Schedule I hereto.

"*GAAP*" means generally accepted accounting principles in the United States.

"*Guarantor*" means each guarantor of the Obligations.

"*Guaranty*" means one or more instruments by which a Guarantor guarantees the Obligations, in form and substance acceptable to Lender.

"*Indebtedness*" means (a) all items of indebtedness or liability which in accordance with GAAP or federal tax law would be included in determining total liabilities as shown on the liabilities side of a balance sheet, (b) indebtedness secured by any mortgage, pledge, lien or security interest existing on property owned by Borrower, whether or not the indebtedness secured thereby shall have been assumed and (c) guaranties and endorsements (other than for purposes of collection in the ordinary course of business) by Borrower and other contingent obligations of Borrower in respect of, or to purchase or otherwise acquire, indebtedness of others.

"*Interim Interest Date*" has the meaning ascribed to such term in Schedule I hereto.

"*Interim Interest Payment Date*" has the meaning ascribed to such term in Schedule I hereto.

"*Lien*" means any security interest, mortgage, pledge, hypothecation, assignment, deposit arrangement, encumbrance, lien (statutory or otherwise), charge against or interest in property to secure payment of a debt or performance of an obligation or other priority or preferential arrangement of any kind or nature whatsoever.

"*Loan*" means a loan from Lender to Borrower pursuant to this Agreement.

"*Loan Documents*" means, collectively, this Agreement, each Note, each Loan Request, any Guaranty and each other instrument or document executed or delivered by Borrower pursuant to or in connection with this Agreement and the other Loan Documents, including, without limitation, any instrument or agreement given to evidence or further secure the Obligations.

"*Loan Request*" means a Loan Request, duly executed by an authorized officer of Borrower, in form and substance acceptable to Lender.

"*Material Adverse Effect*" means a material adverse effect on (a) the business, assets, operations, properties or condition (financial or otherwise) of Borrower or any Guarantor, (b) the ability of Borrower to perform or pay its Obligations or any Indebtedness in the amount of $10,000,000.00 or more in accordance with the terms thereof, (c) the ability of any Guarantor to perform its, his or her obligations under a Guaranty, (d) Lender's Lien on the Collateral or the priority of such Lien, or (e) the validity or enforceability of any Loan Document or the rights and remedies available to Lender under any Loan Document.

"*Maximum Principal Amount*" has the meaning ascribed to such term in Schedule I hereto.

"*Moody's*" means Moody's Investor Services, Inc. or any successor thereto.

"*Note*" has the meaning ascribed to such term in Section 2.02.

"*Notice Address*" has the meaning ascribed to such term in Schedule I hereto.

"*Obligations*" means, subject to Section 8.10(c), the obligations to make the payment of all indebtedness evidenced by the Notes, together with all extensions, renewals, amendments and modifications thereof and the payment of all other Indebtedness and other sums owed under, and the payment and the performance of all obligations and covenants contained in the Loan Documents, in each case whether now existing or hereafter incurred, direct or indirect, absolute or contingent, and due or to become due, together with all fees and expenses (including, without limitation, all attorneys' fees and expenses) incurred by Lender in connection with the collection or enforcement of any of the Obligations.

"*Organizational Documents*" has the meaning ascribed to such term in Schedule I hereto.

"*Original Principal Amount*" means the aggregate principal balance of each Loan as of the Closing Date for such Loan.

"*Payment Date*" has the meaning ascribed to such term in Schedule I hereto.

"*Permitted Liens*" means any of the following: (a) Liens (other than Liens relating to Environmental Laws) for taxes, assessments or other governmental charges not yet due and payable, (b) statutory Liens of landlords, carriers, warehousemen, mechanics, materialmen and other similar Liens imposed by law, which are incurred in the ordinary course of business for sums that are not delinquent, (c) Liens in favor of Lender, and (d) Liens explicitly identified in any Loan Document as "permitted liens."

"*Person*" means any natural person, corporation, partnership, limited liability company, firm, association, trust, government, governmental agency or any other entity, whether acting in an individual, fiduciary or other capacity.

"*Prepayment Fee*" means with respect to each Loan, the prepayment fee described in the related Note.

"S&P" means Standard & Poor's, a division of The McGraw-Hill Companies, Inc. or any successor thereto.

"*Scheduled Commitment Termination Date*" has the meaning ascribed to such term in Schedule I hereto.

"*Stated Maturity Date*" means, with respect to each Loan, the scheduled maturity date described in the related Note.

"*UCC*" means the Uniform Commercial Code as from time to time in effect in the State of New York.

Section 1.02. Rules of Construction. The singular form of any word used herein, including the terms defined in Section 1.01 hereof, shall include the plural, and vice versa. The use herein of a word of any gender shall include correlative words of all genders. Unless otherwise specified, references to Articles, Sections and other subdivisions of this Agreement are to the designated Articles, Sections and other subdivision of this Agreement as originally executed. The words "hereof," "herein," "hereunder" and words of similar import refer to this Agreement as a whole. The headings or titles of the several articles and sections shall be solely for convenience of reference and shall not affect the meaning, construction or effect of the provisions hereof.

Section 1.03. Accounting and Financial Determinations. Unless otherwise specified, all accounting terms used herein or in any other Loan Document shall be interpreted, all accounting determinations and computations hereunder or thereunder shall be made, and all financial statements required to be delivered hereunder or thereunder shall be prepared in accordance with GAAP consistently applied. In the event that GAAP changes during the term of this Agreement such that the financial covenants contained herein would then be calculated in a different manner or with different components, Borrower and Lender shall amend such provisions of this Agreement in such respects as necessary to conform the financial covenants as criteria for evaluating the financial condition of Borrower or a Guarantor, as applicable, to substantially the same criteria as were effective prior to such change in GAAP.

ARTICLE II: THE LOANS

Section 2.01. Loans.

(a) ***Commitment***. Lender hereby agrees, subject to the terms and conditions of this Agreement, to make one or more Loans to Borrower from time to time during the period from the date hereof to the Commitment Termination Date in the aggregate Original Principal Amount not to exceed the Maximum Principal Amount (the "Commitment"). Not more than one Loan shall be funded in any calendar month, and each Loan shall be in an Original Principal Amount of at least $250,000. The Original Principal Amount of each Loan shall reduce, dollar for dollar, the remaining available amount under the Commitment, and any amount funded may not be reborrowed after being repaid. The Commitment shall terminate automatically and without any further action on the Commitment Termination Date. Borrower's obligation to repay a Loan shall commence, and interest shall begin to accrue, on the Closing Date of such Loan.

(b) ***Loan Request***. By delivering a duly completed and executed Loan Request to Lender, on a Business Day, Borrower may irrevocably request that a Loan be made on the Closing Date specified in such Loan Request (which date shall be at least two Business Days but no more than 10 Business Days after the date of delivery to Lender of such Loan Request). On such Closing Date, subject to the terms and conditions contained herein, Lender shall disburse the Original Principal Amount specified in such Loan Request to, or on behalf of, Borrower to the accounts or entities specified in such Loan Request. Such Loan Request shall specify the applicable Closing Date, the Original Principal Amount of such Loan and the applicable disbursement instructions. Borrower agrees that the proceeds of all Loans shall be used solely for the purposes described in such Loan Request.

Section 2.02. Note. Each Loan made by Lender under this Agreement shall be evidenced by, and repaid with interest in accordance with, a single promissory note of Borrower in form and substance acceptable to Lender, duly completed, in the principal amount of the Original Principal Amount of such Loan, dated as of the Closing Date for such Loan, made payable to Lender or order, and maturing on the Stated Maturity Date of such Loan or such earlier date pursuant to an acceleration hereunder (the "Note").

Section 2.03. Scheduled Payments. On each Payment Date, Borrower shall pay the aggregate scheduled principal and interest payments owed with respect to each Loan as set forth in the Notes and any prepayment as provided in Section 2.04; provided, however, on the Stated Maturity Date or date of acceleration of a Loan, Borrower shall repay in full the aggregate then outstanding principal amount of such Loan plus all accrued and unpaid interest thereon and all other amounts owed hereunder or under any other Loan Document related to such Loan.

All amounts required to be paid by Borrower hereunder shall be paid in lawful money of the United States of America in immediately available funds to the following account, or to such other account as designated by Lender to Borrower in writing:

Clearing Bank: RBS Citizens, N.A.
ABA: 241070417
Beneficiary: RBS Asset Finance Customer Payments
Account: 450000-157-2
Borrower: **ISIS Pharmaceuticals, Inc.**

Any payment received after 3:00 p.m. New York time will be deemed to be received on the next succeeding Business Day. Whenever any payment to be made hereunder shall be stated to be due on a day which is not a Business Day, such payment may be made on the next succeeding Business Day, and such extension of time shall in such case be included in the computation of interest or the fees hereunder, as the case may be. All payments shall be applied first to accrued interest and then to principal.

Section 2.04. Prepayments.

(a) ***Voluntary Prepayments***. Prior to the Stated Maturity Date, Borrower may, from time to time on any Payment Date, make a voluntary prepayment of principal outstanding under the Loans; provided, however, that (a) no Loan may be prepaid in part but, instead, if principal outstanding thereunder is prepaid at all, the entire principal balance outstanding thereunder shall be prepaid in full; (b) all such voluntary prepayments shall require notice on or before the date that is 30 calendar days in advance of any prepayment of the Loans; and (c) in connection with each such voluntary prepayment, Borrower shall pay all accrued interest on the outstanding principal amount of the Loan or Loans prepaid, all other amount owed under any Loan Document and, except as otherwise provided in any Loan Document, the aggregate Prepayment Fee for the Loan or Loans prepaid, which shall not be refundable.

(b) ***Mandatory Prepayment Upon Acceleration***. Upon any acceleration of any Loan pursuant to Section 7.02, Borrower shall immediately repay all (or if only a portion is accelerated thereunder, such portion of) the Loans then outstanding, including accrued and unpaid interest thereon, plus the aggregate Prepayment Fee for all such Loans and all other amounts owed under the Loan Documents.

Section 2.05. Interest Provisions.

(a) Interest on the outstanding principal amount of each Loan shall accrue at a rate per annum equal to the Fixed Rate for such Loan. Interest shall be computed on the basis of a 360-day year consisting of 12 30-day months. On the Interim Interest Payment Date for a Loan, Borrower shall pay interest accruing on such Loan from the applicable Closing Date through and including the last day of the calendar month immediately preceding the applicable Interim Interest Date. Interest accruing on each Loan on and after the Interim Interest Date for such Loan shall be payable on each Payment Date or the date of prepayment, as applicable.

(b) Any payment under a Loan Document that is not paid by Borrower on the due date thereof shall, to the extent permissible by law, bear a late charge equal to the lesser of three cents ($.03) per dollar of the delinquent amount or the lawful maximum, and Borrower shall be obligated to pay the same immediately upon receipt of Lender's written invoice therefor.

(c) Upon the occurrence and during the continuation of any Event of Default or after acceleration, Borrower shall pay interest (i) with respect to all Loans at a rate per annum equal to the rate otherwise in effect plus an additional 3% per annum and (ii) with respect to all other Obligations of Borrower to Lender at a rate per annum equal to the highest Fixed Rate then in effect plus an additional 3% per annum (each such rate, a "Default Rate").

(d) The obligations of Borrower hereunder and under the Notes and the other Loan Documents shall be subject to the limitation that payments of interest to Lender, plus any other amounts paid to Lender in connection herewith and therewith, shall not be required to the extent (but only to the extent) that contracting for and receiving such payment by Lender would be contrary to the provisions of any law applicable to Lender limiting the highest rate of interest which may be contracted for, charged or received by Lender, and in such event Borrower shall pay such Lender interest and other amounts at the highest rate permitted by applicable law.

Section 2.06. Payments Absolute. The obligations of Borrower to pay interest and principal required under this Article II and to make other payments under the Loan Documents and to perform and observe the covenants and agreements contained

herein and therein shall be absolute and unconditional in all events, without abatement, diminution, deduction, setoff or defense for any reason, including, without limitation, any failure of the Collateral to be delivered, installed or constructed, as applicable, any defects, malfunctions, breakdowns or infirmities in the Collateral or any accident, condemnation, destruction or unforeseen circumstances. Notwithstanding any dispute between Borrower and Lender or any other person, Borrower shall make all payments under the Loan Documents when due and shall not withhold any payments pending final resolution of such dispute, nor shall Borrower assert any right of set-off or counterclaim against its obligation to make such payments required under the Loan Documents.

ARTICLE III: CONDITIONS TO LOANS

Lender's agreement to make the Loans to Borrower hereunder and to disburse the proceeds thereof shall be subject to the condition precedent that Lender shall have received, on or prior to the applicable Closing Date (or by such other time as may be specified herein with respect thereto), all of the following, each in form and substance satisfactory to Lender:

(a) This Agreement and all other Loan Documents, properly executed on behalf of Borrower, and each of the exhibits and schedules hereto and thereto properly completed.

(b) The respective Note, properly executed on behalf of Borrower.

(c) A Loan Request for each such Loan, duly completed and properly executed on behalf of Borrower.

(d) A certificate of the Secretary or an Assistant Secretary of Borrower, certifying as to (i) the resolutions of the board of directors of Borrower, authorizing the execution, delivery and performance of this Agreement, the Note, the other Loan Documents and any related documents, (ii) the Organizational Documents of Borrower, (iii) the signatures of the officers or agents of Borrower authorized to execute and deliver this Agreement, the Note, the other Loan Documents and other instruments, agreements and certificates on behalf of Borrower, and (iv) no Default or event or circumstance that could reasonably be likely to have a Material Adverse Effect has occurred.

(e) Current certified copies of the Organizational Documents of Borrower.

(f) A Certificate of Good Standing issued as to Borrower by the Secretary of the State of the state of Borrower's organization (or once Borrower has provided a Certificate of Good Standing, a confirmation from a reputable filing service in the applicable jurisdiction that such Good Standing Certificate is still in effect) not more than 30 days prior to the Closing Date.

(g) A Certificate of Qualification issued as to Borrower by the Secretary of the State of the state where the Collateral is or will be located (or once Borrower has provided a Certificate of Qualification, a confirmation from a reputable filing service in the applicable jurisdiction that such Certificate of Qualification is still in effect) not more than 30 days prior to the Closing Date.

(h) [Intentionally Omitted]

(i) [Intentionally Omitted]

(j) [Intentionally Omitted]

(k) [Intentionally Omitted]

(l) Certificates of the insurance required hereunder, containing a lender's loss payable clause in favor of Lender.

(m) [Intentionally Omitted]

(n) Current searches of appropriate filing offices showing that (i) no state or federal tax liens have been filed and remain in effect against Borrower, and (ii) no financing statements have been filed and remain in effect against Borrower relating to the Collateral except those financing statements filed by Lender.

(o) Payment of the Closing Fee and, if any, all of Lender's other fees, commissions and expenses in connection with the funding of each Loan.

(p) [Intentionally Omitted]

(q) Any other documents or items reasonably required by Lender.

ARTICLE IV: REPRESENTATIONS, WARRANTIES AND COVENANTS OF BORROWER

Borrower represents, warrants and covenants for the benefit of Lender, as of the date hereof and each Closing Date, as follows:

(a) Borrower is a corporation duly organized, validly existing and in good standing under the laws of the jurisdiction of its organization. Borrower is in good standing and is duly licensed or qualified to transact business in each jurisdiction where the nature of its business requires such qualification, except for those jurisdictions in which the failure to qualify could not reasonably be expected to have a Material Adverse Effect. Borrower's exact legal name is as set forth on the execution page hereof.

(b) Borrower has full power and authority and holds all requisite governmental licenses, permits and other approvals to (i) enter into and perform its obligations under this Agreement, the Note and each other Loan Document to which it is a party and to own its property, (ii) use the Collateral and (iii) conduct its business substantially as currently conducted by it, except as to clause (iii) where the failure to hold such licenses, permits and approvals could not reasonably be expected to have a Material Adverse Effect.

(c) This Agreement, the Note and the other Loan Documents to which it is a party have been duly authorized, executed and delivered by Borrower and constitute legal, valid and binding obligations of Borrower, enforceable against Borrower in accordance with their respective terms, except to the extent limited by bankruptcy, reorganization or other laws of general application relating to or effecting the enforcement of creditors' rights.

(d) The execution and delivery of this Agreement, the Note and the other Loan Documents, the consummation of the transactions contemplated hereby and thereby and the fulfillment of the terms and conditions hereof and thereof do not and will not violate any law, rule, regulation or order, conflict with or result in a breach of any of the terms or conditions of any Organizational Document of Borrower or of any corporate restriction or of any agreement or instrument to which Borrower is now a party and do not and will not constitute a default under any of the foregoing or result in the creation or imposition of any liens, charges or encumbrances of any nature upon any of the property or assets of Borrower other than Liens in favor of Lender.

(e) The authorization, execution, delivery and performance of this Agreement, the Note and the other Loan Documents by Borrower do not require submission to, approval of, or other action by any governmental authority or agency, except for such action that has been duly obtained or taken and is in full force and effect.

(f) Assuming the timely filing with the Secretary of State of Borrower's State of UCC-1 financing statements showing Borrower as the "debtor" thereunder and Lender as the "secured party" thereunder and containing a description of the Collateral substantially similar to the description of the Collateral contained in the respective Collateral Schedules, each of the Loan Documents that purports to create a security interest creates a valid first priority Lien on the Collateral subject only to Permitted Liens, securing the payment and performance of the Obligations.

(g) Except as disclosed by Borrower in its filings with the SEC that are available to the public, there is no action, suit, proceeding, claim, inquiry or investigation, at law or in equity, before or by any court, regulatory agency, public board or body pending or, to the best of Borrower's knowledge, threatened against or affecting Borrower or any Guarantor, challenging Borrower's or any Guarantor's authority to enter into this Agreement, the Note or any of the other Loan Documents or any other action wherein an unfavorable ruling or finding would adversely affect the enforceability of this Agreement, the Note or any of the other Loan Documents, or could reasonably be expected to have a Material Adverse Effect.

(h) Borrower has good title to all of the Collateral, in each case free and clear of all Liens except for Permitted Liens.

(i) Borrower is in compliance with all laws, rules, regulations and orders of governmental authorities applicable to it and its properties except to the extent the non-compliance with which could not reasonably be expected to have a Material Adverse Effect.

(j) Borrower has heretofore furnished to Lender the Financial Statements and those statements fairly present the financial condition of Borrower and such Guarantor, if any, on the dates thereof and the results of its operations and cash flows for the periods then ended and were prepared in accordance with GAAP. Since the date of the most recent financial statements, there has been no material adverse change in the business, properties or financial condition or prospects of Borrower or any Guarantor. Except as disclosed in the Financial Statements or the notes thereto and for the items previously disclosed in writing by Borrower to Lender, neither Borrower nor any Guarantor, as of each Closing Date, has or will have any liabilities, contingent or otherwise, that could reasonably be expected to have a Material Adverse Effect.

(k) Borrower has filed, and will pay, all federal, state and local tax returns which are required to be filed by it, and Borrower has paid or caused to be paid to the respective taxing authorities all taxes as shown on said returns or on any assessment received by it to the extent such taxes have become due, except any such taxes or charges which are being

diligently contested in good faith by appropriate proceedings and for which adequate reserves in accordance with GAAP have been set aside on its books.

(l) For purposes of Section 9-307 of the UCC, Borrower is and will remain located in the Borrower's State. Borrower's residence for federal income tax purposes is located at its Notice Address specified in Schedule I. Borrower has authorized Lender to file financing statements that are sufficient when filed to perfect the security interests created pursuant to this Agreement and the other Loan Documents. When such financing statements are filed in the offices noted therein, Lender will have a valid and perfected security interest in the Collateral that constitutes personal property, subject to no other Lien other than Permitted Liens.

(m) All factual information heretofor or contemporaneously furnished by or on behalf of Borrower or any Guarantor in writing to Lender for purposes of or in connection with this Agreement or any transaction contemplated hereby is, and all other such factual information hereafter furnished by or on behalf of Borrower or any Guarantor to Lender will be, true and correct in every material respect on the date as of which such information is dated or certified, and such information is not, or shall not be, as the case may be, incomplete by omitting to state any material fact necessary to make such information not misleading.

(n) None of Borrower or any Guarantor is engaged principally, or as one of its important activities, in the business of extending credit for the purpose of purchasing or carrying "margin stock." None of the proceeds of any Loan will be used for the purpose of, or be made available by Borrower or any Guarantor in any manner to any other Person to enable or assist such Person in, directly or indirectly purchasing or carrying "margin stock". Terms for which meanings are provided in F.R.S. Board Regulation T, U or X or any regulations substituted therefor, as from time to time in effect, are used in this Section with such meanings.

(o) None of Borrower or any Guarantor is an "investment company" nor a "company controlled by an investment company" within the meaning of the Investment Company Act of 1940, as amended, or a "holding company," or a "subsidiary company" of a "holding company," or an "affiliate" of a "holding company" or of a "subsidiary company" of a "holding company," within the meaning of the Public Utility Holding Company Act of 1935, as amended.

ARTICLE V: SECURITY INTEREST

This Agreement is intended to constitute a security agreement within the meaning of the UCC. To secure the payment and performance of the Obligations, Borrower hereby grants to Lender a security interest constituting a first Lien on the Collateral. Borrower hereby authorizes, and ratifies any previous authorization for, Lender to file UCC financing statements and any amendments thereto describing the Collateral and containing any other information required by the applicable UCC. Borrower authorizes Lender, and hereby grants Lender a power of attorney (which is coupled with an interest), to file financing statements and amendments thereto securing the Collateral and containing any other information required by the applicable UCC and all proper terminations of the filings of other secured parties with respect to the Collateral, in such form and substance as Lender, in its sole discretion, may determine. Until the later of the Scheduled Commitment Termination Date or the date there is no outstanding Indebtedness under the Notes, Borrower hereby waives any right that Borrower may have to file with the applicable filing officer, and agrees that it will not file or authorize the filing of, any financing statement, amendment, termination or other record pertaining to the Collateral and/or Lender's interest therein, except as authorized by Lender in writing.

ARTICLE VI: COVENANTS

Section 6.01. Affirmative Covenants. So long as any Loan shall remain unpaid, Borrower will comply, and shall cause each Guarantor to comply, with the following requirements unless waived by Lender in writing:

(a) ***Financial Statements***. Borrower shall deliver to Lender for Borrower and each Guarantor respectively: (i) as soon as practicable, and in any event within 45 days after the end of each fiscal quarter (other than the last fiscal quarter), unaudited financial statements including in each instance, balance sheets, income statements, and statements of cash flow, on a consolidated and consolidating basis, as appropriate, and separate profit and loss statements as of and for the quarterly period then ended and for the fiscal year to date, prepared in accordance with GAAP, and certified by Borrower's chief financial officer or such Guarantor's chief financial officer, as applicable, to be true and correct, (ii) as soon as practicable, and in any event within 90 days after the end of each fiscal year, annual audited financial statements, including balance sheets, income statements and statements of cash flow for the fiscal year then ended, on a consolidated and consolidating basis, as appropriate, which have been prepared by the independent accountants of Borrower or such Guarantor, as applicable, in accordance with GAAP and (iii) as soon as practicable, any certifications required by the Securities and Exchange Commission of the United States (the "SEC") or by securities laws applicable to Borrower and each Corporate Guarantor concerning financial statements of Borrower or such Corporate Guarantor, as applicable. Such audited financial statements shall be accompanied by the independent accountant's opinion, which opinion shall be in form generally recognized as "unqualified." Borrower shall be deemed to have complied with the foregoing requirements

with respect to Borrower and/or any Guarantor, as applicable, if such entity files Forms 10-K and 10-Q with the SEC that are publicly available within the time frames set forth above.

(b) ***[Intentionally Omitted]***

(c) ***Notices***. Borrower shall deliver to Lender each of the following:

(i) as soon as possible and in any event within three Business Days after the occurrence of a Default, an Event of Default or an event which could reasonably be expected to result in a Material Adverse Effect, a statement of Borrower setting forth reasonably detailed information regarding such Default, Event of Default or event and the action that Borrower has taken and proposes to take with respect thereto;

(ii) promptly after the commencement thereof, notice in writing of all litigation and of all proceedings before any governmental or regulatory agency affecting Borrower or any Guarantor which seek a monetary recovery against Borrower or any

Guarantor in excess of $10,000,000;

(iii) promptly upon knowledge thereof, notice of any loss, theft or destruction of or material damage to, or and any action, suit or proceeding relating to, Collateral having a value in excess of $250,000;

(iv) promptly after the amending thereof, copies of any and all amendments to any of its Organizational Documents (provided Borrower shall be deemed to have complied with the foregoing requirements with respect to Borrower if Borrower discloses such amendments by filing a Form 8-K with the SEC that is publicly available within the times frames set forth above);

(v) promptly upon knowledge thereof, notice of the violation by Borrower of any law or court order applicable to Borrower, which violation could reasonably be expected to have a Material Adverse Effect.

(d) ***Compliance with Laws***. Borrower shall comply in all material respects with all governmental rules and regulations and all other applicable laws and court orders, including, without limitation, all Environmental Laws.

(e) ***Maintenance of Properties***. Borrower shall, at its own expense, maintain, preserve, protect and keep the Collateral in good repair, working order and condition in compliance with all applicable laws, rules, regulations and the requirements of all applicable insurance policies, and make necessary and proper repairs, renewals and replacements so that its business carried on in connection therewith may be properly conducted at all times and shall maintain in full force and effect all rights, franchises, permits, licenses, trademarks, tradenames, approvals, authorizations, leases and contracts necessary to carry on its business as presently or proposed to be conducted where the failure to so maintain the same could reasonably be expected to have a Material Adverse Effect. Borrower will not make any material alterations, modifications or additions to the Collateral which cannot be removed without materially damaging the functional capabilities or economic value of the Collateral unless Lender has provided its prior written consent.

(f) ***Insurance***. Borrower shall, at its own expense, procure and maintain continuously in effect: (i) public liability insurance for personal injuries, death or damage to or loss of property arising out of or in any way relating to the Collateral, and (ii) insurance against such hazards as Lender may reasonably require, in each case in amounts reasonably acceptable to Lender. All insurance policies required by this Section shall be taken out and maintained with insurance companies reasonably acceptable to Lender. Borrower shall provide written notice to Lender of any cancellation or material revision of coverage under any such insurance at least 30 days before the cancellation or revision becomes effective. No insurance shall be subject to any co-insurance clause. Borrower shall cause Lender to be named as loss payee on all insurance policies relating to any Collateral and shall cause Lender to be named as additional insured under all liability policies, in each case pursuant to appropriate endorsements in form and substance satisfactory to Lender. Such insurance shall not be affected by any unintentional act or negligence or representation or warranty on the part of Borrower or other owner of the policy or the property described in such policy. Prior to each Closing Date, Borrower shall deposit with Lender evidence satisfactory to Lender of such insurance and, at least 10 days prior to the expiration thereof, Borrower will promptly notify Lender, if such insurance is cancelled (but no later than 30 days following such cancellation. At Lender's request, Borrower shall provide Lender evidence reasonably satisfactory to Lender of such insurance. Borrower shall provide or cause to be provided to Lender and to its insurance consultant (or any agent, officer or employee of Lender) such other information relating to its insurance coverage as may be reasonably requested by Lender.

(g) ***Books and Records; Inspections***. Borrower will keep books and records that accurately reflect all of its material business affairs and transactions. Borrower will, and will cause each Guarantor to, permit Lender or any of its representatives (including outside auditors), upon reasonable advance written notice and at reasonable times (not to exceed two Business Days) and intervals (which intervals, so long as no Default or Event of Default exists, shall not exceed more than one visit in any 12 month period, but if a Default or Event of Default exists, shall be unlimited), to visit all of its offices, to discuss its financial matters with its officers and to reasonably examine (and, at the expense of

Borrower, copy extracts from) books or other corporate records (including computer records), provided however, if an Event of Default exist Lender shall not be required to provide any such advance written notice to Borrower.

(h) ***Perfection of Liens***. Borrower shall take such action as may be necessary or as Lender may request in order to perfect and protect Lender's Lien on the Collateral.

(i) ***Title***. Borrower will at all times protect and defend, at its own cost and expense, its title from and against all claims, liens and legal processes of creditors of Borrower (other than Lender), and keep all Collateral free and clear of all such claims, liens and processes other than Permitted Liens.

Section 6.02. Negative Covenants. So long as the Loan shall remain unpaid, Borrower agrees that:

(a) ***Liens***. Borrower will not create, incur or suffer to exist any mortgage, deed of trust, pledge, lien, security interest, assignment or transfer in, on or of any of the Collateral except for Permitted Liens.

(b) ***Fundamental Changes***. Borrower will not, without Lender's prior written consent, enter into any merger, consolidation, reorganization, or recapitalization, or reclassify its capital stock, or liquidate, wind up, or dissolve itself (or suffer any liquidation or dissolution), or, other than in the ordinary course of its business, convey, sell assign, lease, transfer, or otherwise dispose of, in one transaction or series of transactions, all or any substantial part of its property or assets; provided, however, that notwithstanding the foregoing, Borrower may enter into a merger or consolidation or convey, sell assign, lease, transfer, or otherwise dispose of, in one transaction or series of transactions, all or any substantial part of its property or assets without Lender's prior written consent if the surviving or acquiring entity in such transaction (i) (A) shall be organized and existing under the laws of the United States or any state thereof, or (B) shall, both before and after giving effect to such transaction, have assets in the United States of $100,000,000.00 or more, (ii) shall promptly execute and deliver to Lender an agreement reasonably satisfactory to Lender pursuant to which such entity assumes and agrees to be fully liable for all of Borrower's obligations under the Loan Documents, and (iii) (A) shall have it's senior unsecured debt rated by S&P and Moody's, and (B) such senior unsecured debt shall be rated at least BBB by S&P and at least Baa2 by Moody's, and, in such case, after giving effect to such transaction, no other Default or Event of Default shall exist.

(c) ***Sale of Collateral***. Borrower will not (in each case in one transaction or series of related transactions) sell, transfer, lease, contribute or otherwise convey or dispose of, or grant options, warrants or other rights with respect to, or agree to do any of the foregoing with respect to, all or any part of the Collateral.

(d) ***Location or Name Changes***. Borrower will not change its location for purposes of Section 9-307 of the UCC or its name in any manner that could make any financing statement filed in connection with any Loan Document seriously misleading within the meaning of Section 9-506 of the UCC or any similar statute, unless it shall have given Lender at least 30 days' prior written notice thereof.

(e) ***Replacement Cash Collateral***. At any time during the term hereof, Borrower shall be permitted to deposit with and pledge to Lender (or one of its affiliates), as security for the Obligations, cash or cash equivalents in a sum equal to the principal amount of the Loans outstanding from time to time, plus the unused portion of the Maximum Principal Amount all on terms and conditions reasonably satisfactory to Lender and Borrower. In the event Borrower pledges such cash collateral with Lender (or one of its affiliates) on terms and conditions satisfactory to Lender, then Lender shall release its security interest in the Collateral; provided, however, that Lender shall not be obligated to release its security interest in the Collateral prior to the expiration of the applicable period described in Section 547 of the United State Bankruptcy Code (11 U.S.C. §547) or any other similar law or regulation or any successor to any such law for avoiding (or otherwise setting aside) the cash collateral pledge.

Section 6.03. Indemnity.

(a) Whether or not covered by insurance, Borrower hereby assumes responsibility for and agrees to reimburse Lender, its affiliates and its and their respective officers, directors, employees and agents (individually and collectively, the "Indemnified Parties") for and will indemnify, defend and hold the Indemnified Parties harmless from and against all liabilities, obligations, losses, damages, penalties, claims, suits, actions, proceedings, judgments, awards, amounts paid in settlements, obligations, debts, diminutions in value, fines, penalties, charges, fees, costs and expenses (including reasonable attorneys' fees and expenses) of whatsoever kind and nature, imposed on, incurred by or asserted against any Indemnified Party that in any way relate to or arise out of any of the Loan Documents, the transactions contemplated thereby or the Collateral, including, without limitation (collectively, the "Losses"), (i) the selection, manufacture, construction, acquisition, acceptance or rejection of the Collateral, (ii) the ownership of the Collateral, (iii) the delivery, installation, lease, possession, maintenance, use, condition, return or operation of the Collateral, (iv) the condition of the Collateral sold or otherwise disposed of after possession by Borrower, (v) any patent or copyright infringement, (vi) any act or omission on the part of Borrower, Guarantor or any of its or their officers, employees,

agents, contractors, lessees, licensees or invitees, (vii) any misrepresentation or inaccuracy in any representation or warranty of Borrower or any Guarantor, or a breach of Borrower or any Guarantor of any of its covenants or obligations under any of the Loan Documents, (viii) any claim, loss, cost or expense involving alleged damage to the environment relating to the Collateral, including, without limitation, investigation, removal, cleanup and remedial costs, (ix) any personal injury, wrongful death or property damage arising under any statutory or common law or tort law theory, including, without limitation, damages assess for the maintenance of a private or public nuisance or for the conducting of an abnormally dangerous activity on or near the Collateral, (x) any past, present or threatened, in writing, injury to, or destruction of, the Collateral, including, without limitation, costs to investigate and assess such injury or damage and (xi) any administrative process or proceeding or judicial or other similar proceeding (including, without limitation, any alternative dispute resolution process and any bankruptcy proceeding) in any way connected with any matter addressed in any of the Loan Documents; provided however, that Borrower shall not be required to indemnify, defend or hold harmless any Indemnified Party from and against Losses to the extent arising from Indemnified Party's gross negligence or willful misconduct.

(b) An Indemnified Party shall provide prompt written notice to Borrower of a possible indemnification claim after the Indemnified Party receives notice of the claim, provided however, that the failure of an Indemnified Party to provide prompt written notice to Borrower shall not release Borrower from any obligations under this Section except to the extent Borrower is materially prejudiced by such failure. If any action or proceeding be commenced, to which action or proceeding one or more of the Indemnified Parties are made a party by reason of the execution or performance of this Agreement or any other Loan Document, or in which it becomes necessary to defend or uphold the Lien of this Agreement, all sums paid by the Indemnified Parties, for the expense of any litigation to prosecute or defend the rights and Lien created hereby or otherwise, shall be paid by Borrower to such Indemnified Parties, as the case may be, as hereinafter provided. Borrower will pay and save the Indemnified Parties harmless against any and all liability with respect to any intangible personal property tax or similar imposition of any state or any subdivision or authority thereof now or hereafter in effect, to the extent that the same may be payable by the Indemnified Parties in respect of this Agreement or any Obligation.

(c) All amounts payable to Indemnified Parties under this Section shall be deemed Obligations secured by this Agreement and shall be payable immediately upon demand. In case any action, suit or proceeding is brought against one or more of the Indemnified Parties by reason of any such occurrence, Borrower, upon request of such Indemnified Parties, will, at Borrower's expense, resist and defend such action, suit or proceeding or cause the same to be resisted or defended by counsel designated by Borrower, which counsel shall be reasonably acceptable to Lender, and Borrower shall have full power to litigate, compromise or settle the same on behalf of the Indemnified Parties in its sole discretion; *provided* that (i) Borrower shall have acknowledged in writing its obligation to fully indemnify such Indemnified Parties in respect of such action, suit or proceeding prior to assuming the defense thereof, (ii) Borrower shall keep such Indemnified Parties fully apprised of the status of such action, suit or proceeding and shall provide such Indemnified Parties with all information with respect to such action, suit or proceeding as such Indemnified Parties shall reasonably request, (iii) each such Indemnified Party, at its own expense, may participate in any action, suit or proceeding controlled by Borrower and (iv) no such settlement shall include an admission of an omission or misconduct of an Indemnified Party without the prior written consent of such Indemnified Party. In connection with any claim for indemnification hereunder by an Indemnified Party, such Indemnified Party shall cooperate in good faith with Borrower. Notwithstanding anything in this Section to the contrary, Borrower shall not be entitled to control and assume, or continue, the defense of, or compromise or settle, any action, suit or proceeding if (A) an Event of Default shall have occurred and be continuing, (B) in the reasonable opinion of such Indemnified Parties, such action, suit or proceeding will involve any material danger of the sale, forfeiture or loss of, or creation of any Lien on any Collateral, (C) in the reasonable opinion of such Indemnified Parties, there exists an actual or potential conflict of interests, (D) such claim or liability involves the risk of criminal sanctions or liability to any such Indemnified Party or (E) such proceeding involves claims against an Indemnified Party not fully indemnified by Borrower or which Borrower and the Indemnified Parties have been unable to sever such claims from the indemnified claim(s). In the circumstances described in clauses (A) through (E), such Indemnified Parties shall be entitled to control or defend such action, suit or proceeding at the expense of Borrower; provided, however, that no Indemnified Party shall be permitted to settle or compromise any action, suit or proceeding without the prior written consent of Borrower, which consent shall not be unreasonably withheld, conditioned or delayed. Borrower may in any event participate in all such actions, suits or proceedings at its own expense.

Nothing herein contained shall be deemed to require an Indemnified Party to contest any liability, charge, loss, obligation, claim, damage, penalty, cause of action, suit, cost, expense or judgment or assume control of or defend any action, suit or proceeding with respect thereto. The obligations of Borrower under this Section shall survive the termination of this Agreement and not be merged with any applicable judgment. If and to the extent that the foregoing undertaking may be unenforceable for any reason, Borrower hereby agrees to make the maximum contribution to the payment and satisfaction of each of the Losses that is permissible under applicable law.

Section 6.04. Performance by Lender. If Borrower at any time fails to perform or observe any of the covenants or agreements contained in this Agreement, Lender may, but need not, with notice to Borrower, perform or observe such covenant on behalf and in the name, place and stead of Borrower (or, at Lender's option, in Lender's name) and may, but need not, take any and all other actions which Lender may reasonably deem necessary to cure or correct such failure (including, without limitation, the payment of taxes, the satisfaction of security interests, liens or encumbrances, the performance of obligations owed to account debtors or other obligors, the procurement and maintenance of insurance, the execution of assignments, security agreements and financing statements, and the endorsement of instruments), and Borrower shall thereupon pay to Lender on demand the amount of all moneys expended and all costs and expenses (including reasonable attorneys' fees and legal expenses) incurred by Lender in connection with or as a result of the performance or observance of such agreements or the taking of such action by Lender, together with interest thereon from the date expended or incurred at the lesser of the highest Default Rate then in effect or the highest rate permitted by law.

ARTICLE VII: EVENTS OF DEFAULT

Section 7.01. Events of Default. Each of the following events or occurrences shall constitute an "Event of Default":

(a) Borrower shall default in the payment of any Obligation when due and such failure continues for 10 calendar days;

(b) Any representation or warranty of Borrower made in any Loan Document or any other writing or certificate furnished by or on behalf of Borrower pursuant to any Loan Document is or shall be incorrect when made in any material respect;

(c) Borrower shall fail to perform any of its obligations under Section 6.01(c), 6.01(f), 6.01(i) or 6.02(a);

(d) Borrower shall default in the due performance and observance of any other agreement contained herein or in any other Loan Document (other than items set forth elsewhere in this Section 7.01), and such default shall continue unremedied for a period of 30 days after Borrower has actual knowledge thereof or has received notice by Lender thereof;

(e) The occurrence of an event of default or a breach or default, after the passage of all applicable notice and cure or grace periods provided therefor, under any other Loan Document or any other agreement between or among Borrower or any Guarantor and Lender or any of its affiliates;

(f) The occurrence of a default or an event of default (however defined) under any instrument, agreement or other document evidencing or relating to, and the acceleration of, any indebtedness or other monetary obligation of Borrower or any Guarantor having a principal amount (including, without limitation, the amount of any outstanding letters of credit), individually or in the aggregate, in excess of $10,000,000;

(g) (i) Any judgment or order for the payment of money (not paid or fully covered by insurance maintained in accordance with the requirements of this Agreement and as to which the relevant insurance company has acknowledged coverage) in excess of $10,000,000 shall be rendered against Borrower or any Guarantor, which judgment or order is not, within thirty (30) days after entry thereof, bonded or stayed pending appeal, or (ii) any such judgment or order (not paid or fully covered by insurance maintained in accordance with the requirements of this Agreement and as to which the relevant insurance company has acknowledged coverage) becomes a final, unappealable judgment or order;

(h) The occurrence of any Change in Control unless the Person or group (as such term is used in Section 13(d)(3) of the Exchange Act) acquiring such control, or the Person with control of such Person, (i) shall have it's senior unsecured debt rated by S&P and Moody's, and (ii) such senior unsecured debt shall be rated at least BBB by S&P and at least Baa2 by Moody's, and the Person that has such senior unsecured debt ratings shall have executed and delivered to Lender a guaranty of all of Borrower 's obligations and liabilities under the Loan Documents, which guaranty shall be in form and substance satisfactory to Lender;

(i) Borrower or any Guarantor shall be or become insolvent, or admit in writing its inability to pay its debts as they mature, or make an assignment for the benefit of creditors; or Borrower or any Guarantor shall apply for or consent to the appointment of any receiver, trustee or similar officer for it or for all or any substantial part of its property; or such receiver, trustee or similar officer shall be appointed without the application or consent of Borrower or any Guarantor (and such involuntary appointment is not dismissed or stayed within 30 days); or Borrower or any Guarantor shall institute (by petition, application, answer, consent or otherwise) any bankruptcy, insolvency, reorganization, arrangement, readjustment of debt, dissolution, liquidation or similar proceeding relating to it under the laws of any jurisdiction; or any such proceeding shall be instituted (by petition, application or otherwise) against Borrower or any Guarantor (and such involuntary proceeding is not dismissed or stayed within 30 days; or

(j) Any Loan Document or any Lien granted thereunder shall (except in accordance with its terms), in whole or in part, terminate, cease to be effective or cease to be the legally valid, binding and enforceable obligation of

Borrower; Borrower or any Guarantor or any other Person shall, directly or indirectly, contest in any manner the effectiveness, validity, binding nature or enforceability of any Loan Document or any Lien granted thereunder; or any Lien securing (or required to secure) any Obligation shall, in whole or in part, cease to be a first priority perfected Lien subject only to Permitted Liens.

(k) At any time Borrower shall be a guarantor of obligations under such Loan Agreement, an of Event of Default shall exist under and as defined in that certain Loan Agreement of even date herewith between Lender and IBIS BIOSCIENCES, INC.

(l) [Intentionally Omitted]

Section 7.02. Remedies. (a) Following the occurrence of an Event of Default described in subsection (i) of Section 7.01, all of the outstanding principal amount of the Loans and other Obligations shall be due and payable and the Commitment (if not theretofore terminated) shall terminate, whereupon the full unpaid amount of such Loans and other Obligations which shall be so declared due and payable shall be and become immediately due and payable, without presentment, notice of dishonor, protest or further notice of any kind, all of which are hereby expressly waived by Borrower, and, as the case may be, the Commitment shall terminate.

(b) Following the occurrence of any Event of Default and subject to subsection (a) of this Section, Lender may exercise, at its option, concurrently, successively or in any combination, all rights and remedies of a secured party in, to and against the Collateral granted by the UCC or otherwise available at law or in equity, including, without limitation:

(i) by notice to Borrower, declare all or any portion of the outstanding principal amount of the Loans and other Obligations to be due and payable and/or the Commitment (if not theretofore terminated) to be terminated, whereupon the full unpaid amount of such Loans and other Obligations which shall be so declared due and payable shall be and become immediately due and payable, without presentment, notice of dishonor, protest or further notice of any kind, all of which are hereby expressly waived by Borrower, and/or, as the case may be, the Commitment shall terminate;

(ii) recover all fees and expenses (including, without limitation, reasonable attorneys' fees) in connection with the lawful collection or enforcement of the Obligations, which fees and expenses shall constitute additional Obligations of Borrower hereunder;

(iii) take immediate and exclusive possession of the Collateral, which constitutes personal property, or any part thereof, with or without any court order or other process of law and enter the premises where such Collateral is located and remove the same therefrom, or require Borrower to assemble and package such Collateral and make it available to Lender for its possession at a place designated by Lender;

(iv) sell, lease, sublease, hold or otherwise dispose of all or any part of the Collateral and hold, maintain, preserve and prepare the Collateral for sale until disposed of;

(v) [Intentionally Omitted]

(vi) sue for specific performance of any Obligation or recover damages for breach thereof; and

(vii) exercise any one or more of the remedies available under any Loan Document.

Section 7.03. Use of Proceeds. Any proceeds received by Lender in exercising the rights and remedies specified in Section 7.02 shall be first applied to pay the costs and expenses, including, without limitation, reasonable attorneys' fees and expenses, incurred by Lender as a result of an Event of Default. Any proceeds remaining after payment of such costs and expenses shall be applied to the satisfaction of the Obligations as determined by Lender in its sole discretion and, unless Lender accepts the Collateral in full or partial satisfaction of the Obligations, any excess proceeds after satisfaction of all Obligations shall be paid to Borrower.

ARTICLE VIII: MISCELLANEOUS PROVISIONS

Section 8.01. Waivers, Amendments. No provision of this Agreement or any of the other Loan Documents shall be deemed waived or amended except by a written instrument setting forth the matter waived or amended and signed by the party against which enforcement of such waiver or amendment is sought. Waiver of any matter shall not be deemed a waiver of the same or any other matter on any future occasion. No notice to or demand on Borrower in any case shall entitle it to any notice or demand in similar or other circumstances.

Section 8.02. Notices. All notices, certificates, requests, demands and other formal communications provided for hereunder or under any Loan Document shall be in writing and shall be (a) personally delivered or (b) sent by overnight courier of national reputation, and shall be deemed to have been given on (i) the date received if personally delivered and (ii) the next Business Day if sent by overnight courier. All communications shall be addressed to the party to whom notice is being given at its

Notice Address. If notice to Borrower of any intended disposition of the Collateral or any other intended action is required by law in a particular instance, such notice shall be deemed commercially reasonable if given (in the manner specified in this Section) at least 10 calendar days prior to the date of intended disposition or other action. The parties acknowledge and agree that routine or informal communications may be conducted by email, in addition to the means set forth above.

Section 8.03. Severability. Any provision of this Agreement or any other Loan Document which is invalid, illegal or unenforceable in any jurisdiction shall, as to such provision and such jurisdiction, be ineffective to the extent of such invalidity, illegality or unenforceability without invalidating the remaining provisions of this Agreement or such Loan Document or affecting the validity, legality or enforceability of such provision in any other jurisdiction.

Section 8.04. Execution in Counterparts. This Agreement may be executed in several counterparts, each of which shall be an original and all of which shall constitute one and the same document.

Section 8.05. Further Assurance and Corrective Instruments. Borrower hereby agrees that it will, from time to time, execute, acknowledge and deliver or authorize, as applicable, or cause to be executed, acknowledged and delivered or authorized, such further acts, instruments, conveyances, transfers

and assurances and take such other actions, as Lender reasonably deems necessary or advisable for the implementation, correction, confirmation or perfection of this Agreement or the other Loan Documents and any rights of Lender hereunder or thereunder.

Section 8.06. Time of the Essence. Time is of the essence with respect to the performance by Borrower of the Obligations.

Section 8.07. Entire Agreement. This Agreement and the other Loan Documents constitute the entire agreement between Lender and Borrower. There are no other understandings, agreements, representations or warranties, written or oral, between Lender and Borrower with respect to the subject matter of this Agreement and the other Loan Documents.

Section 8.08. Governing Law. THIS AGREEMENT AND THE NOTES SHALL EACH BE DEEMED TO BE A CONTRACT MADE UNDER AND GOVERNED BY THE INTERNAL LAWS OF THE STATE OF ILLINOIS, WITHOUT REGARD TO THE CONFLICT OF LAWS PRINCIPLES THEREOF.

Section 8.09. Successors and Assigns; Assignments by Lender. This Agreement shall be binding upon and shall inure to the benefit of the parties hereto and their respective successors and assigns; provided, however, that Borrower may not assign or transfer its rights or obligations hereunder without the prior written consent of Lender except as permitted under Section 6.02(b). Lender may assign, in whole or in part, its rights under this Agreement. Upon any assignment by Lender of its entire right and interest under the Loan Documents, Lender shall automatically be relieved, from and after the date of such assignment, of any liability for the performance of any obligation of Lender therein.

Section 8.10. Assignments and Participations. Borrower acknowledges and agrees that a material inducement to Lender's willingness to complete the transactions contemplated by the Loan Documents is that Lender may, at any time, complete an assignment or participation with respect to any Loan Document or any or all of the servicing rights with respect thereto. In connection with any such assignment or participation: (a) Borrower agrees to cooperate in good faith with Lender, including, without limitation, providing such documents, financial information and other information ("Information") reasonably requested by Lender or any entity involved with respect to such assignment or participation; (b) Borrower consents to Lender's providing the Information, including any other information that Lender may now have or hereafter acquire with respect to Borrower or the Collateral to any entity involved with respect to such assignment or participation; and (c) Notwithstanding anything to the contrary in any Loan Document, in the event that Lender assigns a Note, (i) the related Loan shall be deemed a separate loan that includes and incorporates each term and condition in this Agreement and the other Loan Documents related thereto, (ii) the term "Obligations" as used herein and in the Loan Documents with respect to any assignee shall mean only the Indebtedness and obligations evidenced by or related to the Notes held by the assignee and (iii) the term Collateral as used herein and in the Loan Documents with respect to such assignee shall mean only the Collateral described on the Collateral Schedules that specifically refer to the Notes held by such assignee.

Section 8.11. Waiver of Jury Trial. LENDER AND BORROWER HEREBY WAIVE THEIR RESPECTIVE RIGHTS TO A JURY TRIAL OF ANY CLAIM OR CAUSE OF ACTION BASED UPON OR ARISING OUT OF, DIRECTLY OR INDIRECTLY, THIS AGREEMENT, ANY OF THE LOAN DOCUMENTS, ANY DEALINGS BETWEEN LENDER AND BORROWER RELATING TO THE SUBJECT MATTER OF THE TRANSACTIONS CONTEMPLATED BY THIS AGREEMENT OR ANY LOAN DOCUMENT, AND/OR THE RELATIONSHIP THAT IS BEING ESTABLISHED BETWEEN LENDER AND BORROWER. BORROWER ACKNOWLEDGES AND AGREES THAT THIS PROVISION IS A MATERIAL INDUCEMENT FOR LENDER ENTERING INTO THIS AGREEMENT AND THE OTHER LOAN DOCUMENTS. THE SCOPE OF THIS WAIVER IS INTENDED TO BE ALL ENCOMPASSING OF ANY AND ALL DISPUTES THAT MAY BE FILED IN ANY COURT (INCLUDING, WITHOUT LIMITATION, CONTRACT CLAIMS, TORT CLAIMS, BREACH OF DUTY CLAIMS AND ALL OTHER COMMON LAW AND STATUTORY CLAIMS). THIS WAIVER IS IRREVOCABLE, MEANING THAT IT MAY NOT BE MODIFIED EITHER ORALLY OR IN WRITING, AND THIS WAIVER SHALL APPLY

TO ANY SUBSEQUENT AMENDMENTS, RENEWALS, SUPPLEMENTS OR MODIFICATIONS TO THIS AGREEMENT, ANY LOAN DOCUMENT, OR TO ANY OTHER DOCUMENT OR AGREEMENT RELATING TO THE TRANSACTIONS CONTEMPLATED BY THIS AGREEMENT OR ANY RELATED TRANSACTION. IN THE EVENT OF LITIGATION, THIS AGREEMENT MAY BE FILED AS A WRITTEN CONSENT TO A TRIAL BY THE COURT.

Section 8.12. Forum Selection and Consent to Jurisdiction. BORROWER AND LENDER HEREBY IRREVOCABLY SUBMIT TO THE JURISDICTION OF ANY FEDERAL OR LOCAL COURT LOCATED IN THE CITY OF CHICAGO, ILLINOIS, AND ANY APPELLATE COURT FROM ANY THEREOF, IN ANY ACTION, SUIT OR PROCEEDING BROUGHT AGAINST IT AND TO OR IN CONNECTION WITH THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREUNDER OR FOR RECOGNITION OR ENFORCEMENT OF ANY JUDGMENT; PROVIDED, HOWEVER, THAT ANY SUIT SEEKING ENFORCEMENT AGAINST ANY COLLATERAL OR OTHER PROPERTY MAY BE BROUGHT, AT LENDER'S OPTION, IN THE COURTS OF ANY JURISDICTION WHERE SUCH COLLATERAL MAY BE FOUND. BORROWER HEREBY EXPRESSLY AND IRREVOCABLY SUBMITS TO THE JURISDICTION OF SUCH COURTS FOR THE PURPOSE OF ANY SUCH LITIGATION AS SET FORTH ABOVE. BORROWER FURTHER IRREVOCABLY CONSENTS TO THE SERVICE OF PROCESS BY REGISTERED MAIL, POSTAGE PREPAID, OR BY PERSONAL SERVICE WITHIN OR WITHOUT THE STATE OF ILLINOIS. BORROWER HEREBY EXPRESSLY AND IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY LAW, ANY OBJECTION WHICH IT MAY HAVE OR HEREAFTER MAY HAVE TO THE LAYING OF VENUE OF ANY SUCH LITIGATION BROUGHT IN ANY SUCH COURT REFERRED TO ABOVE AND ANY CLAIM THAT ANY SUCH LITIGATION HAS BEEN BROUGHT IN AN INCONVENIENT FORUM. TO THE EXTENT THAT BORROWER HAS OR HEREAFTER MAY ACQUIRE ANY IMMUNITY FROM JURISDICTION OF ANY COURT FROM ANY LEGAL PROCESS (WHETHER THROUGH SERVICE OR NOTICE, ATTACHMENT PRIOR TO JUDGMENT, ATTACHMENT IN AID OF EXECUTION OR OTHERWISE) WITH RESPECT TO ITSELF OR ITS PROPERTY, BORROWER HEREBY IRREVOCABLY WAIVES SUCH IMMUNITY IN RESPECT OF ITS OBLIGATIONS UNDER THIS AGREEMENT AND THE OTHER LOAN DOCUMENTS.

Section 8.13. Waiver of Certain Claims. TO THE EXTENT PERMITTED BY APPLICABLE LAW, BORROWER AND EACH GUARANTOR SHALL NOT ASSERT, AND HEREBY WAIVES, ANY CLAIM AGAINST LENDER ON ANY THEORY OF LIABILITY FOR SPECIAL, INDIRECT, CONSEQUENTIAL OR PUNITIVE DAMAGES (AS OPPOSED TO DIRECT OR ACTUAL DAMAGES) ARISING OUT OF, IN CONNECTION WITH, OR AS A RESULT OF, ANY LOAN DOCUMENT OR ANY AGREEMENT OR INSTRUMENT CONTEMPLATED THEREBY, ANY LOAN OR THE USE OF THE PROCEEDS THEREOF.

[REMAINDER OF PAGE INTENTIONALLY BLANK; EXECUTION PAGE FOLLOWS.]

RBS Asset Finance

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their respective officers thereunto duly authorized as of the day and year first above written.

BORROWER:

By /s/ B. Lynne Parshall
Name B. Lynne Parshall
Title COO & CFO

LENDER:

RBS ASSET FINANCE, INC.

By /s/ Cynthia Prince
Name Cynthia Prince
Title Vice President

[EXECUTION PAGE OF LOAN AGREEMENT]

RBS Asset Finance

SCHEDULE I

The following terms shall have the following meanings:

"*Borrower's State*" means Delaware.

"*Closing Fee*" — Not applicable

"*Financial Statements*" means the audited financial statement of Borrower and each Guarantor for their fiscal years ended December 31, 2007 and the unaudited financial statement of Borrower and each Guarantor and for the quarter ended June 30, 2008.

"*Fixed Rate*" means, with respect to each Loan and each Note, a rate per annum equal to the sum of (i) the notional rate per annum for a fixed rate payer under a 3 year interest rate swap on the day that is two Business Days prior to the applicable Closing Date plus (ii) (a) 3.85% or (b) such other amount as Lender may specify, which rate will be set forth in such Note.

"*Interim Interest Date*" means, with respect to each Loan and each Note, the interim interest date described in such Note.

"*Interim Interest Payment Date*" means, with respect to each Loan and each Note, the interim interest date described in such Note.

"*Maximum Principal Amount*" means $9,400,000.00.

"*Notice Address*" means with respect to Borrower or Lender, as applicable, the following address, or such other address as such party may designate in writing to the other party:

If to Borrower:
Isis Pharmaceuticals, Inc.
Attention: Chief Financial Officer
1896 Rutherford Road
Carlsbad, CA 92008
Telephone No.: 760 603-2469
Facsimile No.: 760 918-3592

w/copy to General Counsel (fax: 760 268-4922

If to Lender:
RBS Asset Finance, Inc.
71 S. Wacker Drive, Suite 2800
Chicago, IL 60606
Telephone No.: (312) 777-3500
Facsimile No.: (312) 777-4001

"*Organizational Documents*" means (i) with respect to Borrower, the articles of incorporation and by-laws of Borrower and (ii) with respect to each Corporate Guarantor, the articles of incorporation and by-laws/certificate of formation and limited liability company/operating agreement] of such Guarantor.

"*Payment Date*" means the first Business Day of each calendar month.

"*Scheduled Commitment Termination Date*" means March 31, 2009.

REGULUS THERAPEUTICS LLC

EMPLOYMENT AGREEMENT

This **EMPLOYMENT AGREEMENT** (the "**Agreement**") is made and entered into effective as of December 29, 2008 by and between Regulus Therapeutics LLC, a Delaware limited liability corporation (the "**Company**"), and Kleanthis G. Xanthopoulos, Ph.D. (the **"Executive"**). The Company and the Executive are hereinafter collectively referred to as the "**Parties**", and individually referred to as a "**Party**".

The Company desires assurance of the association and services of the Executive in order to retain the Executive's experience, skills, abilities, background and knowledge, and is willing to engage the Executive's services on the terms and conditions set forth in this Agreement.

The Parties previously entered into a letter agreement dated November 30, 2007 (the "**Prior Agreement**") and desire to terminate and replace the Prior Agreement with this Agreement, except as set forth herein.

The Executive desires to be in the employ of the Company, and is willing to accept such employment on the terms and conditions set forth in this Agreement.

AGREEMENT

In consideration of the foregoing recitals and the mutual promises and covenants herein contained, and for other good and valuable consideration, the Parties, intending to be legally bound, agree as follows:

1. EMPLOYMENT.

1.1 Term. The term of this Agreement shall begin on the date first set forth above (the "**Effective Date**"), and shall continue until terminated in accordance with Section 4 herein.

1.2 Title. The Executive shall have the title of Chief Executive Officer of the Company and shall serve in such other capacity or capacities as the Board of Directors of the Company (the "**Board**") may from time to time prescribe, but only as consistent with the customary duties of a Chief Executive Officer. During the term of this Agreement, unless otherwise agreed by the Parties, the Executive shall also serve as a member of the Board. Upon termination of the Executive's employment with the Company, for any reason or no reason, the Executive shall immediately resign as a member of the Board.

1.3 Duties. The Executive shall report to the Board and shall do and perform all reasonable services, acts or things necessary or advisable to manage and conduct the business of the Company and which are normally associated with the position of Chief Executive Officer, consistent with the bylaws of the Company and as required by the Board.

1.4 Location. The Executive shall perform services pursuant to this Agreement at the Company's offices located in Carlsbad, California, or at any other place at which the Company maintains an office; provided, however, that (i) the Company will not relocate the offices that are the primary location at which the Executive performs services pursuant to this Agreement by more than thirty miles from the then current location without the Executive's prior written consent and (ii) the Company may from time to time require the Executive to travel temporarily to other locations in connection with the Company's business.

2. LOYAL AND CONSCIENTIOUS PERFORMANCE; NONCOMPETITION.

2.1 Loyalty. During the Executive's employment by the Company the Executive shall devote the Executive's full business energies, interest, abilities and productive time to the proper and efficient performance of the Executive's duties under this Agreement.

2.2 Covenant not to Compete. Except with the prior written consent of the Board, the Executive will not, while employed by the Company, or during any period during which the Executive is receiving compensation or any other consideration from the Company, including, but not limited to, severance pay pursuant to Section 4.1.3 herein, engage in competition with the Company and/or any of its affiliates, subsidiaries, or joint ventures currently existing or which shall be established during the Executive's employment by the Company (collectively, "**Affiliates**") either directly or indirectly, in any manner or capacity, as adviser, principal, agent, affiliate, promoter, partner, officer, director, employee, stockholder, owner, co-owner, consultant, or member of any association or otherwise, in any phase of the business of developing, manufacturing and marketing of products or services which are in the same field of use or which otherwise compete with the products or services or proposed products or services of the Company or any of its Affiliates.

2.3 Agreement not to Participate in Company's Competitors. During his employment by the Company, the Executive agrees not to acquire, assume or participate in, directly or indirectly, any position, investment or interest known by the Executive to be adverse or antagonistic to the Company, its business or prospects, financial or otherwise or in any company, person or entity that is, directly or indirectly, in competition with the business of the Company or any of its Affiliates. Ownership by the Executive, as a passive investment, of less than 2% of the outstanding shares of capital stock of any corporation with one or more classes of its capital stock listed on a national securities exchange or in the over-the-counter market shall not constitute a breach of this paragraph.

3. COMPENSATION OF THE EXECUTIVE.

3.1 Base Salary. The Company shall pay the Executive a base salary of $420,000 per year (the "**Base Salary**"), less payroll deductions and all required withholdings, payable in regular bi-weekly payments or otherwise in accordance with Company policy. Such Base Salary shall be prorated for any partial year of employment on the basis of a 365-day fiscal year.

3.2 Discretionary Bonuses. In addition to the Base Salary, the Executive will be eligible to receive a yearly discretionary merit bonus (with a base percentage factor of forty percent (40%)) in accordance with the Company's Executive Bonus Plan to be established by the Company based upon the Executive's performance, as determined by the Board in its sole discretion, against fundamental objectives to be mutually agreed upon by the Executive and the Board. Any bonus that is earned by the Executive under the Executive Bonus Plan, or any other bonus plan approved by the Board, shall be paid to the Executive no later than the March 15 of the year immediately following the year in which such bonus was earned.

3.3 Stock Options. The Company agrees that it will grant to the Executive, pursuant to the terms of the Company's 2009 Equity Incentive Plan (the "**Plan**") to be established by the Company following the Company's conversion to a Delaware corporation, stock options to purchase shares of the Common Stock of the Company (each an "**Option**" and collectively, the "**Options**") representing five percent (5%) of the shares of capital stock of the Company outstanding following the Series A Preferred Stock Financing of the Company (which is expected to occur in the first fiscal quarter of 2009) determined on a fully-diluted, as converted to Common Stock basis, including shares reserved for issuance pursuant to the Plan. Such Options shall include an "early-exercise" feature, which will allow the Executive to exercise the Options with respect to some or all of the unvested shares and such unvested shares shall thereafter be subject to a repurchase option in favor of the Company, which repurchase option shall lapse in accordance with the stated vesting of such unvested Options. To the maximum extent possible, the Options shall be "incentive stock options" as such term is defined in Section 422 of the Internal Revenue Code of 1986, as amended (the "**Code**"). The purchase price of the shares issuable upon exercise of the Options shall be equal to the fair market value per share of the Company's Common Stock on the date of grant, as determined in good faith by the Board based on a valuation performed by a qualified independent appraiser using a traditional appraisal methodology. The Options will be subject to vesting over a period of four (4) years following the grant date, with 1/4th of the shares subject to such Options vesting on the one (1) year anniversary of the grant date and 1/48th of the shares subject to such Options vesting on a monthly basis thereafter until all the shares subject to such Options are vested on the fourth anniversary of the grant date, in each case only so long as the Executive remains continuously employed by the Company. In the event of a Change in Control (as defined below), regardless of termination of the Executive's employment, the vesting of the Options set forth in Section 3.3 hereof shall accelerate and vest in full. The terms and vesting of the Options will be more fully set forth in the Plan and shall be subject to the Company's standard form of stock option agreement.

3.4 Changes to Compensation. It is anticipated that the Executive will be considered on an annual basis for merit increases in base compensation consistent with performance and market trends but subject to Board approval in its sole discretion. Subject to Section 4.1.3 below, the Executive's compensation may be changed from time to time in the Company's sole discretion based upon Board approved changes to the Company's operating plan after considering relevant business conditions.

3.5 Employment Taxes. All of the Executive's compensation and payments under this Agreement shall be subject to customary withholding taxes and any other employment taxes as are commonly required to be collected or withheld by the Company.

3.6 Benefits. The Executive shall, in accordance with Company policy and the terms of the applicable plan documents, be eligible to participate in benefits under any executive benefit plan or arrangement which may be in effect from time to time and made available to the Company's executive or key management employees.

3.7 Vacations and Holidays. The Executive shall be entitled to receive three (3) weeks of paid vacation during each calendar year, and shall be entitled to paid holidays in accordance with the Company's policies.

4. TERMINATION.

4.1 Termination By the Company. The Executive's employment with the Company may be terminated under the following conditions:

4.1.1 Termination for Death or Disability. The Executive's employment with the Company shall terminate effective upon the date of the Executive's death or Complete Disability (as defined below). If the Executive's employment shall be terminated by death or Complete Disability, the Company shall pay to the Executive, and/or the Executive's heirs, the Executive's Base Salary and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings, and the Company shall thereafter have no further obligations to the Executive and/or the Executive's heirs under this Agreement.

4.1.2 Termination by the Company For Cause. The Company may terminate the Executive's employment under this Agreement for Cause (as defined below) or the Executive may resign his employment under this Agreement without Good Reason (as defined below). If the Executive's employment shall be terminated by the Company for Cause or by the Executive without Good Reason, the Company shall pay the Executive's Base Salary and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings, and the Company shall thereafter have no further obligations to the Executive under this Agreement.

4.1.3 Termination By The Company Without Cause Or By The Executive With Good Reason. If the Company (or its successor) terminates the Executive's employment without Cause, or if the Executive terminates his employment for Good Reason, then the Company shall pay the Executive's Base Salary and accrued and unused vacation benefits earned through the date of termination at the rate in effect at the time of termination, less standard deductions and withholdings. In addition, subject to the Executive's delivery to the Company of a release and waiver of claims in the form attached hereto as **Exhibit A** within the applicable time period set forth therein, but in no event later than forty-five (45) days following termination of Executive's employment, and permitting such Release and Waiver to become

fully effective in accordance with its terms, (the date Executive's Release becomes fully effective, the "**Release Effective Date**"), the Company shall provide the Executive with the following benefits hereunder, as applicable (the "**Severance Benefits**"):

4.1.3.1 If the Executive's termination occurs prior to and not within one month of a Change of Control, the Executive shall be entitled to 18 months of his Base Salary in effect as of the termination date (ignoring any reduction in salary that is the basis for a the Executive's termination of employment for Good Reason), less required deductions and withholdings, paid in the form of salary continuation on the Company's standard payroll dates following termination; provided, however, no such payments will be made prior to the Release Effective Date, and on the first regular payroll date following the Release Effective Date, the Company will pay the Executive in a lump sum the amount of the salary continuation he would have otherwise received on and prior to such date but for the delay due to the Release, with the balance paid thereafter on the original schedule.

4.1.3.2 If the Executive's termination occurs within one month of, or within 12 months following, the effective date of a Change in Control, the Executive shall be entitled to 24 months of his Base Salary in effect as of the termination date (ignoring any reduction in salary that is the basis for a Good Reason Resignation) and two times the maximum amount of the discretionary bonus payable for the then-current year as if all milestones or other performance targets had been achieved, less required deductions and withholdings, paid in the form of a lump sum on the first regular payroll date following the Release Effective Date.

4.1.3.3 The Company shall pay the premiums (the "**COBRA Premiums**") for group health plan continuation coverage (i.e., medical, dental and vision insurance) under Title X of the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("**COBRA**"), under the same plans available to active Company employees and under the same rules, restrictions and regulations applicable thereto for up to 18 months following the Executive's employment termination date or until the Executive becomes eligible for group health insurance coverage through a new employer or otherwise cease to be eligible for COBRA coverage, whichever occurs first; *provided*, that the Executive timely elects continued group health coverage under COBRA and otherwise qualifies for continued coverage. COBRA premium payments extending past 18 months following the Executive's separation from service, to the extent subject to Section 409A (as defined below), shall be made in compliance with Section 409A.

4.1.3.4 The vesting of the Options set forth in Section 3.3 hereof shall accelerate and vest in full.

4.2 Termination by Mutual Agreement of the Parties. The Executive's employment pursuant to this Agreement may be terminated at any time upon mutual agreement, in writing, of the Parties. Any such termination of employment shall have the consequences specified in such writing.

4.3 Survival of Certain Provisions. Sections 2.2, 5 and 17 shall survive the termination of this Agreement.

4.4 Definitions. For purposes of this Agreement:

4.4.1 "**Cause**" shall have the meaning defined in the Plan.

4.4.2 "**Change of Control**" shall mean the occurrence of any one (1) or more of the following events: (i) any person (within the meaning of Section 13(d) or 14(d) of the Securities Exchange Act of 1934, as amended) becomes the owner, directly or indirectly, of securities of the Company representing more than fifty percent (50%) of the combined voting power of the Company's then outstanding securities (other than in connection with a transaction involving the issuance of securities by the Company the principal purpose of which is to raise capital for the Company) other than Isis Pharmaceuticals, Inc. or Alnylam Pharmaceuticals; (ii) there is consummated a merger, consolidation or similar transaction to which the Company is a party and the stockholders of the Company immediately prior thereto do not own outstanding voting securities representing more than fifty percent (50%) of the combined outstanding voting power of the surviving entity immediately following such merger, consolidation or similar transaction or more than fifty percent (50%) of the combined outstanding voting power of the parent of the surviving entity immediately following such merger, consolidation or similar transaction; (iii) there is consummated a sale, lease exclusive license or other disposition of all or substantially all of the consolidated assets of the Company and its subsidiaries, other than a sale, lease or other disposition of all or substantially all of the consolidated assets of the Company and its subsidiaries to an entity more than fifty percent (50%) of the combined voting power of which is owned immediately following such disposition by the stockholders of the Company immediately prior thereto or (iv) prior to December 31, 2009, any of (i), (ii), or (iii) occur with respect to Isis Pharmaceuticals, Inc. or Alnylam Pharmaceuticals.

4.4.3 "**Complete Disability**" shall mean the inability of the Executive to perform the Executive's duties under this Agreement because the Executive has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. In the event the Company has no policy of disability income insurance covering employees of the Company in force when the Executive becomes disabled, the term Complete Disability shall mean the inability of the Executive to perform the Executive's duties under this Agreement by reason of any incapacity, physical or mental, which the Board, based upon medical advice or an opinion provided by a licensed physician acceptable to the Board, determines to have incapacitated the Executive from satisfactorily performing all of the Executive's usual services for the Company for a period of at least 120 consecutive days or 150 days in total during any 12 month period (whether or not consecutive). Based upon such medical advice or opinion, the determination of the Board shall be final and binding and the date such determination is made shall be the date of such Complete Disability for purposes of this Agreement.

4.4.4 "**Good Reason**" for the Executive to terminate the Executive's employment hereunder shall mean the occurrence of any of the following events without the Executive's consent; provided however, that any resignation by the Executive due to any of the following conditions shall only be deemed for Good Reason if: (i) the Executive gives the Company written notice of the intent to terminate for Good Reason within ninety (90) days following the first occurrence of the condition(s) that the Executive believes constitutes Good

Reason, which notice shall describe such condition(s); (ii) the Company fails to remedy, if remediable, such condition(s) within thirty (30) days following receipt of the written notice (the "**Cure Period**") of such condition(s) from the Executive; and (iii) Executive actually resigns his employment within the first fifteen (15) days after expiration of the Cure Period:

4.4.4.1 a material breach of this Agreement with the Executive by the Company;

4.4.4.2 a material reduction by the Company of the Executive's Base Salary as initially set forth herein or as the same may be increased from time to time;

4.4.4.3 a material reduction in the Executive's authority, duties or responsibilities; or

4.4.4.4 the Company relocates the facility that is the Executive's principal place of business with the Company to a location that requires an increase in the Executive's one-way driving distance by more than 30 miles.

5. CONFIDENTIAL AND PROPRIETARY INFORMATION; NONSOLICITATION.

5.1 As a condition of employment the Executive agrees to abide by the Employee Confidential Information and Inventions Agreement entered into between the Company and the Executive as referenced in the Prior Agreement.

5.2 While employed by the Company and for one year thereafter, the Executive agrees that in order to protect the Company's trade secrets and confidential and proprietary information from unauthorized use, the Executive will not, either directly or through others, solicit or attempt to solicit any employee, consultant or independent contractor of the Company to terminate his or her relationship with the Company in order to become an employee, consultant or independent contractor to or for any other person or business entity.

6. ASSIGNMENT AND BINDING EFFECT.

This Agreement shall be binding upon and inure to the benefit of the Executive and the Executive's heirs, executors, personal representatives, assigns, administrators and legal representatives. Because of the unique and personal nature of the Executive's duties under this Agreement, neither this Agreement nor any rights or obligations under this Agreement shall be assignable by the Executive. This Agreement shall be binding upon and inure to the benefit of the Company and its successors, assigns and legal representatives.

7. CHOICE OF LAW.

This Agreement shall be construed and interpreted in accordance with the internal laws of the State of California.

8. INTEGRATION.

This Agreement, including **Exhibit A** and the Employee Confidential Information and Inventions Agreement referenced in Section 5.1, contains the complete, final and exclusive agreement of the Parties relating to the terms and conditions of the Executive's employment and the termination of the Executive's employment, and supersedes all prior and contemporaneous oral and written employment agreements or arrangements between the Parties including the Prior Agreement except as indicated herein.

9. AMENDMENT.

This Agreement cannot be amended or modified except by a written agreement signed by the Executive and the Chief Executive Officer of the Company as directed by the Board.

10. WAIVER.

No term, covenant or condition of this Agreement or any breach thereof shall be deemed waived, except with the written consent of the Party against whom the wavier is claimed, and any waiver or any such term, covenant, condition or breach shall not be deemed to be a waiver of any preceding or succeeding breach of the same or any other term, covenant, condition or breach.

11. SEVERABILITY.

The finding by a court of competent jurisdiction of the unenforceability, invalidity or illegality of any provision of this Agreement shall not render any other provision of this Agreement unenforceable, invalid or illegal. Such court shall have the authority to modify or replace the invalid or unenforceable term or provision with a valid and enforceable term or provision which most accurately represents the Parties' intention with respect to the invalid or unenforceable term or provision.

12. INTERPRETATION; CONSTRUCTION.

The headings set forth in this Agreement are for convenience of reference only and shall not be used in interpreting this Agreement. This Agreement has been drafted by legal counsel representing the Company, but the Executive has been encouraged to consult with, and have consulted with, the Executive's own independent counsel and tax advisors with respect to the terms of this Agreement. The Parties acknowledge that each Party and its counsel has reviewed and revised, or had an opportunity to review and revise, this Agreement, and any rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement.

13. REPRESENTATIONS AND WARRANTIES.

The Executive represents and warrants that the Executive is not restricted or prohibited, contractually or otherwise, from entering into and performing each of the terms and covenants contained in this Agreement, and that the Executive's execution and performance of this Agreement will not violate or breach any other agreements between the Executive and any other person or entity.

14. COUNTERPARTS; FACSIMILE.

This Agreement may be executed in two counterparts, each of which shall be deemed an original, all of which together shall contribute one and the same instrument. Facsimile signatures shall be treated the same as original signatures.

15. LITIGATION COSTS.

Should any claim be commenced between the Parties or their personal representatives concerning any provision of this Agreement or the rights and duties of any person in relation to this Agreement, the Party prevailing in such action shall be entitled, in addition to such other relief as may be granted to a reasonable sum as and for that Party's attorney's fees in such action.

16. TRADE SECRETS.

It is the understanding of both the Company and the Executive that the Executive shall not divulge to the Company and/or its subsidiaries any confidential information or trade secrets belonging to others, including the Executive's former employers, nor shall the Company and/or its Affiliates seek to elicit from the Executive any such information. Consistent with the foregoing, the Executive shall not provide to the Company and/or its Affiliates, and the Company and/or its Affiliates shall not request, any documents or copies of documents containing such information.

17. ADVERTISING WAIVER.

The Executive agrees to permit the Company and/or its Affiliates, and persons or other organizations authorized by the Company and/or its Affiliates, to use, publish and distribute advertising or sales promotional literature concerning the products and/or services of the Company and/or its Affiliates, or the machinery and equipment used in the provision thereof, in which the Executive's name and/or pictures of the Executive taken in the course of the Executive's provision of services to the Company and/or its Affiliates, appear. The Executive hereby waives and releases any claim or right the Executive may otherwise have arising out of such use, publication or distribution. The Company agrees that, following termination of the Executive's employment, it will not create any new such literature containing the Executive's name and/or pictures without the Executive's prior written consent.

18. APPLICATION OF SECTION 409A.

Notwithstanding anything to the contrary set forth herein, any Severance Benefits that constitute "deferred compensation" within the meaning of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect ("**Section 409A**") shall not commence in connection with the Executive's termination of employment unless and until the Executive has also incurred a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h)) ("**Separation From Service**"), unless the Company reasonably determines that such amounts may be provided to the Executive without causing the Executive to incur the additional 20% tax under Section 409A.

It is intended that each installment of the Severance Benefit payments provided for in this Agreement is a separate "payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2)(i). For the avoidance of doubt, it is intended that payments of the Severance Benefits set forth in this Agreement satisfy, to the greatest extent possible, the exemptions from the application of Section 409A provided under Treasury Regulation Sections 1.409A-1(b)(4), 1.409A-1(b)(5) and 1.409A-1(b)(9). However, if the Company (or, if applicable, the successor entity thereto) determines that the Severance Benefits constitute "deferred compensation" under Section 409A and the Executive is, on the termination of service, a "specified employee" of the Company or any successor entity thereto, as such term is defined in Section 409A(a)(2)(B)(i) of the Code, then, solely to the extent necessary to avoid the incurrence of the adverse personal tax consequences under Section 409A, the timing of the Severance Benefit payments shall be delayed until the earlier to occur of: (i) the date that is six months and one day after the Executive's Separation From Service, or (ii) the date of the Executive's death (such applicable date, the "**Specified Employee Initial Payment Date**") and the Company (or the successor entity thereto, as applicable) shall (A) pay to the Executive a lump sum amount equal to the sum of the Severance Benefit payments that the Executive would otherwise have received through the Specified Employee Initial Payment Date if the commencement of the payment of the Severance Benefits had not been so delayed pursuant to this Section and (B) commence paying the balance of the Severance Benefits in accordance with the applicable payment schedules set forth in this Agreement.

19. PARACHUTE PAYMENTS.

Except as otherwise provided in an agreement between the Executive and the Company, if any payment or benefit the Executive would receive from the Company or otherwise in connection with a Change of Control ("**Payment**") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "**Excise Tax**"), then such Payment shall be equal to the Reduced Amount (as defined herein). The "**Reduced Amount**" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax, or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Executive's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a

reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the following order: (1) reduction of cash payments; (2) cancellation of accelerated vesting of equity awards other than stock options; (3) cancellation of accelerated vesting of stock options; and (4) reduction of other benefits paid to the Executive. If acceleration of vesting of compensation from the Executive's equity awards is to be reduced, such acceleration of vesting shall be cancelled in the reverse order of the date of grant.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the date first above written.

REGULUS THERAPEUTICS LLC

By: /s/ John Maraganore.

Name: John Maraganore, Ph.D.

Title: Chairman of the Board

/s/ Kleanthis G. Xanthopoulos, Ph.D.
KLEANTHIS G. XANTHOPOULOS, PH.D.

[SIGNATURE PAGE TO EMPLOYMENT AGREEMENT]

EXHIBIT A

RELEASE AND WAIVER OF CLAIMS

In consideration of the payments and other benefits set forth in Section 4 of the Employment Agreement dated December 29, 2008, to which this form is attached (the **"Employment Agreement"**), I, Kleanthis G. Xanthopoulos, Ph.D., hereby furnish Regulus Therapeutics LLC (the **"Company"**) with the following release and waiver (**"Release and Waiver"**).

In exchange for the consideration provided to me by the Employment Agreement that I am not otherwise entitled to receive, I hereby generally and completely release the Company and its directors, officers, employees, shareholders, partners, agents, attorneys, predecessors, successors, parent and subsidiary entities, insurers, affiliates, and assigns from any and all claims, liabilities and obligations, both known and unknown, that arise out of or are in any way related to events, acts, conduct, or omissions occurring prior to my signing this Release and Waiver. This general release includes, but is not limited to: (1) all claims arising out of or in any way related to my employment with the Company or the termination of that employment; (2) all claims related to my compensation or benefits from the Company, including, but not limited to, salary, bonuses, commissions, vacation pay, expense reimbursements, severance pay, fringe benefits, stock, stock options, or any other ownership interests in the Company; (3) all claims for breach of contract, wrongful termination, and breach of the implied covenant of good faith and fair dealing; (4) all tort claims, including, but not limited to, claims for fraud, defamation, emotional distress, and discharge in violation of public policy; and (5) all federal, state, and local statutory claims, including, but not limited to, claims for discrimination, harassment, retaliation, attorneys' fees, or other claims arising under the federal Civil Rights Act of 1964 (as amended), the federal Americans with Disabilities Act of 1990, the federal Age Discrimination in Employment Act of 1967 (as amended) (**"ADEA"**), and the California Fair Employment and Housing Act (as amended).

I also acknowledge that I have read and understand Section 1542 of the California Civil Code which reads as follows: "**A general release does not extend to claims which the creditor does not know or suspect to exist in his favor at the time of executing the release, which if known by him must have materially affected his settlement with the debtor.**" I hereby expressly waive and relinquish all rights and benefits under that section and any law of any jurisdiction of similar effect with respect to any claims I may have against the Company.

I acknowledge that, among other rights, I am waiving and releasing any rights I may have under ADEA, that this Release and Waiver is knowing and voluntary, and that the consideration given for this Release and Waiver is in addition to anything of value to which I was already entitled as an executive of the Company. If I am 40 years of age or older upon execution of this Release and Waiver, I further acknowledge that I have been advised, as required by the Older Workers Benefit Protection Act, that: (a) the release and waiver granted herein does not relate to claims under the ADEA which may arise after this Release and Waiver is executed; (b) I should consult with an attorney prior to executing this Release and Waiver; (c) I have 21 days in which to consider this Release and Waiver (although I may choose voluntarily to execute this Release and Waiver earlier); (d) I have seven days following the execution of this Release and Waiver to revoke my consent to this Release and Waiver; and (e) this Release and Waiver shall not be effective until the eighth day after I execute this Release and Waiver and the revocation period has expired.

I acknowledge my continuing obligations under my Employee Confidentiality and Inventions Assignment Agreement a copy of which is attached hereto (the **"CIAA"**). Pursuant to the CIAA, I understand that among other things, I must not use or disclose any confidential or proprietary information of the Company and I must immediately return all Company property and documents (including all embodiments of proprietary information) and all copies thereof in my possession or control. I understand and agree that my right to the severance pay I am receiving is in exchange for my agreement to the terms of this Release and Waiver and is contingent upon my continued compliance with my CIAA.

This Release and Waiver, including the CIAA, constitutes the complete, final and exclusive embodiment of the entire agreement between the Company and me with regard to the subject matter hereof. I am not relying on any promise or representation by the Company that is not expressly stated herein. This Release and Waiver may only be modified by a writing signed by both me and a duly authorized officer of the Company.

Date: _____ By: _____
KLEANTHIS G. XANTHOPOULOS

EXHIBIT 10.40

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

C O N F I D E N T I A L

PRE-CLINICAL DEVELOPMENT COLLABORATION AGREEMENT

This Pre-Clinical Development Collaboration Agreement (this "Agreement") is entered into effective as of March 23, 2007 (the "Effective Date") by and between **Isis Pharmaceuticals, Inc.**, a Delaware corporation ("Isis") and **Korea Institute of Toxicology**, a Korean government-established institute for non-clinical research ("KIT").

WHEREAS, Isis designs and develops drugs and, from time to time, requires the performance of certain Pre-Clinical Development (as defined below), including pre-clinical experiments in which a drug is analyzed *in vitro* and/or administered to animal subjects, the results of which are intended to be submitted to or held for inspection by a Regulatory Authority, and KIT has substantial experience and expertise in supporting and conducting such Pre-Clinical Development;

WHEREAS, Isis has amassed significant experience and expertise in the science of preclinical development studies with oligonucleotide therapeutics, a rapidly expanding field of scientific inquiry and source of new drugs and Isis is willing to share that expertise with KIT;

WHEREAS, the Parties wish to utilize their respective expertise to collaborate and conduct Pre-Clinical Development on antisense oligonucleotide drugs (ASOs) created by Isis;

NOW, THEREFORE, in consideration of both the foregoing premises and the terms and conditions set forth below, the Parties hereto agree as follows:

1. DEFINITIONS

1.1 Definitions. When used in this Agreement or any PCD Program (as defined below), capitalized terms not otherwise defined in this Agreement or a PCD Program will have the meanings set forth in Exhibit A, which is attached hereto and made a part hereof.

2. SCOPE OF COLLABORATION AND PCD PROGRAMS

2.1. Scope. The Parties wish to collaborate for pre-clinical pharmacokinetic and toxicology Studies designed to meet the safety regulations for filing an IND as well as any additional Studies required by a Regulatory Authority, Ethics Committee, or institutional review board as a prerequisite to filing an IND ("Level 1 Development"). In the process of running these Studies it is anticipated that Isis will provide specific expertise and technical know-how to aid KIT in performing these and other studies with oligonucleotide therapeutics agents and biotechnology-derived drug candidates in the future. Isis has initially selected its [***] drug for inclusion in this Level 1 Development collaboration and may propose additional drugs for inclusion in the collaboration for Level 1 Development.

2.2. Pre-Clinical Development Plan ("PCD Plan"). The Parties intend to conduct their collaborative activities in accordance with the guidelines of the PCD Plan attached hereto as Exhibit B.

2.3. Pre-Clinical Development Program ("PCD Program"). A PCD Program is an agreement that sets forth the particular Studies that will be performed by KIT for a specific Study Drug agreed to by both Isis and KIT in writing. Exhibit C attached to this Agreement contains a form PCD

Program. The PCD Program will include Protocol(s) which sets forth with specificity how each Study will be performed, which will be drafted by KIT and agreed to by Isis.

3. PERFORMANCE OF RESEARCH

3.1. Technology Transfer. Isis will transfer to KIT relevant expertise or experiences for running pre-clinical toxicology and pharmacokinetics Studies for oligonucleotides and other biotechnology-derived drug candidates, including the bioanalytical methods technology that is necessary to successfully perform the PCD Program(s), which the Parties expect will include:

- [***];
- [***];
- [***];
- [***];
- [***];
- [***];
- [***];
- [***]; and

- [***].

KIT will use certain of these methods, technology and expertise to perform the PCD Program(s). In addition, KIT will have the right to use the expertise acquired for running toxicology studies for oligonucleotide therapeutics, and to adapt Isis' bioanalytical methods used in PCD Program(s) so that KIT can [***].

3.2. Performance. KIT and Isis will each perform its obligations under all PCD Programs in accordance with high professional standards generally accepted in the industry.

3.3. Compliance with Protocol and Laws. KIT will perform its obligations under all PCD Programs in compliance with the Protocol applicable to a Study, all applicable laws, rules and regulations of the jurisdiction in which a Study is conducted or is to be used, as well as the requirements of any Regulatory Authority. KIT agrees to comply with all current applicable Good Laboratory Practice regulations as set forth in 21 C.F.R. Part 58, as amended (including retention/preservation obligations thereunder).

3.4. Quality Control; Personnel.

3.4.1. Throughout the term of any PCD Program, KIT will maintain appropriate internal and external quality control and monitoring measures (including those required by 21 C.F.R. Part 11) to ensure proper performance of Pre-Clinical Development.

3.4.2. When performing its obligations under a PCD Program, KIT will use only those of its employees, consultants and agents (including the Identified Employee) who have

sufficient experience, education, training, expertise and other qualifications to perform Pre-Clinical Development at the highest professional level.

3.4.3. In light of the mutual goal and understanding between the Parties that the Pre-Clinical Development will be used for submission(s) to Regulatory Authorities, Ethics Committees, and institutional review boards, including for registration of INDs for studies in humans, each Party further represents and agrees that neither it, nor its respective employees, Affiliates or agents have ever been (i) debarred, or (ii) convicted of a crime for which a person can be debarred, under subsection (a) or (b) of 21 U.S.C. § 335a, as amended, and each Party agrees that it does not now and will not in the future use in any capacity the services of any person debarred under subsection (a) or (b) of 21 U.S.C. § 335a, as amended. If during the term of this Agreement, a Party or any other person performing Pre-Clinical Development hereunder (i) becomes debarred or disqualified, or (ii) receives notice of an action or threat of an action with respect to debarment or disqualification, such Party will immediately notify the other Party.

3.5. Destruction. The Parties agree that Confidential Information will be preserved and retained until mutual agreement of the Parties to destroy or otherwise dispose of it.

3.6. Inquiries. In furtherance of the collaborative relationship created by this Agreement, the Parties will promptly respond to reasonable questions and requests from one another regarding any Pre-Clinical Development and make available, upon reasonable notice, its respective employees, consultants and agents to meet with the other Party, its representatives and/or representatives of any Regulatory Authority.

4. CORESPONDENCE WITH REGULATORY AUTHORITIES

4.1. KIT will notify Isis immediately (and in any event within 24 hours) in writing or by email (i) if any Regulatory Authority inspects, requests an inspection, or makes written or oral inquiries regarding any aspect of a Study and (ii) of any violation or deficiency regarding a Study noted by any Regulatory Authority.

4.2. KIT will provide Isis as soon as reasonably practicable (but in any event within 5 days) with a copy of all correspondence between KIT and any Regulatory Authority regarding any aspect of a Study. KIT will provide Isis a copy of any proposed response to any Regulatory Authority that relates to a Study for Isis' review prior to submission, and KIT agrees to incorporate Isis' comments to such response.

5. INSPECTIONS

KIT will allow Isis and any Regulatory Authority (including their respective employees, consultants and agents) to inspect each location at which Pre-Clinical Development is performed.

6. COMPENSATION; EXPENSES; INSTRUMENTATION

6.1. Compensation. Subject to Section 12 below, as consideration for timely performance of Pre-Clinical Development under any and all PCD Program(s) and in support of the expense of the Identified Employee, Isis will pay KIT, within fifteen (15) days following execution of this Agreement, the sum of [***] and thereafter, Isis will make an additional payment of [***] (the "Isis Funding"). In addition, Isis will reimburse KIT for certain costs and expenses as set forth in each applicable PCD Program. Other than Isis Funding and reimbursement by Isis for agreed

upon costs and expenses, KIT will pay any costs required to conduct the Pre-Clinical Development in accordance with each PCD Program.

6.2. Procedure. KIT will invoice Isis on each payment date, and such invoice will be due within thirty (30) days of Isis' receipt of such invoice.

6.3. Currency. Amounts set forth in each PCD Program and all invoices will be in U.S. dollars and payment by Isis will be made in U.S. dollars.

6.4. [***]. Isis agrees to provide to KIT, in consideration for performance of Pre-Clinical Development under this Agreement, the following [***] in Isis' possession ("[***]") for use by KIT in performance of Pre-Clinical Development:

(i) [***]; and

(ii) [***].

Isis is providing this [***] to KIT, and KIT accepts such [***], in its "as is" condition. Isis disclaims any and all warranties (whether expressed or implied) with respect to the [***], including any warranties of fitness for a particular purpose, merchantability, suitability for use in performance of Pre-Clinical Development, or non-infringement. KIT agrees to indemnify Isis from and against any liability arising from use of the [***].

Isis will notify KIT when [***] is available for shipment. The [***] will be shipped by Isis to KIT, EXW (Incoterms 2000), Isis' premises, to the destination specified in writing by KIT. All shipping and insurance costs are the responsibility of KIT.

7. ROYALTIES; ROYALTY TERM; MILESTONE PAYMENT.

7.1. Royalties. (a) If [***], then Isis will pay KIT a royalty of [***]% of the Net Sales of any Product containing such Study Drug.

(b) Alternate Royalty Rate. If [***], the royalty rate will be less than [***]% and will be specified in the PCD Program; *provided*, *however*, in such event the PCD Program must be signed by Isis' Chief Executive Officer or Chief Financial Officer. If [***], the Parties will negotiate an appropriate alternative royalty rate that is less than a [***]% royalty rate and that is based on [***]. In any case, if [***], Isis will not have an obligation to pay any royalty to KIT.

7.2. Royalty Term. (a) With respect to Product(s) that are subject to a bona fide agreement between Isis and a third-party for the commercialization of such Product(s), Isis' obligation to pay royalties to KIT under Section 7.1 above will begin upon [***] and will continue so long as [***]. In addition, the specific aspects of royalty payment timing, payment method, currency, records retention, audit rights, and other material commercial terms customarily applicable to royalties will be handled by the Parties in the manner set forth in applicable underlying contracts between Isis and third-parties for Product(s), and the Parties agree to cooperate in good faith, using the spirit and intent of such underlying contracts, to address any issues between the Parties relevant to royalties that are not otherwise dealt with in such contracts.

(b) With respect to Product(s) that Isis is commercializing on its own and not pursuant to a bona fide commercialization agreement with a third-party, Isis' obligation to pay royalties to KIT under Section 7.1 above, will (on a country-by-country basis) begin upon [***] and will continue so

long as [***]. The specific aspects of royalty payment timing, payment method, currency, records retention, audit rights, and other material commercial terms customarily applicable to royalties will be handled in accordance with Exhibit D.

7.3 Milestone Payment. If [***], then Isis will pay KIT a milestone payment of $[***]. This $[***] milestone payment to KIT will be fully creditable toward any future royalties payable by Isis to KIT.

8. MATERIALS

8.1. Ownership. All right title and interest in to and under any material, compound, or product (including any derivation thereof) provided by Isis or its employees, consultants and/or agents under this Agreement or any PCD Program or acquired by KIT in the course of providing Pre-Clinical Development ("Materials") will be and remain the property of Isis.

8.2. Obligations. KIT will (a) hold all Materials in strict confidence and take all reasonable precautions to protect the Materials, (b) not transfer the Materials or divulge any information derived therefrom to any third person, including any affiliated entity, (c) not make any use whatsoever at any time of the Materials (other than to perform Pre-Clinical Development) and (d) not analyze the composition of matter or sequence of the Materials. Any employees, consultants and agents of KIT given access to the Materials must have a legitimate need for access and will be bound in writing to restrictions no less restrictive than those set forth in this Section 8.2. KIT will be responsible to Isis for any violations of this Section 8.2 by such individuals/entities.

9. STUDY INVENTIONS AND DATA

9.1. Existing Property. All Inventions, Intellectual Property Rights and other technology owned by a Party as of the Effective Date will remain the separate property of such Party and no licenses or other rights (whether by implication, estoppel or otherwise) with respect to such Inventions, Intellectual Property Rights or other technology are granted to any other party except as expressly set forth in this Agreement. All employees, consultants and agents of KIT will be bound in writing to substantially the same obligations imposed on KIT as set forth in this Section 9.1.

9.2. Ownership. All right title and interest in to and under (a) any Inventions conceived, created, discovered or developed (whether directly or indirectly) solely by either Party or jointly by the Parties from performing under this Agreement or a PCD Program and (b) any results, information or documents arising, resulting or generated (whether directly or indirectly) solely by either Party or jointly by the Parties from performing under this Agreement or a PCD Program (collectively, the "Program Data") will be and remain the property of Isis, except for KIT Methods. KIT and Isis agree that they will each execute and deliver or cause the execution and delivery of all such documents, certificates, assignments and other writings, and take such other actions as may be necessary or desirable or requested by the other Party, to vest in such Party the ownership rights granted hereunder. All employees, consultants and agents of KIT will be bound in writing to substantially the same obligations imposed on KIT as set forth in this Section 9.2. KIT will be responsible to Isis for any violations of this Section 9.2 by any employees, consultants and agents of KIT.

9.3. Disclosure. KIT agrees that it will (a) notify Isis, promptly following conception, creation, discovery, development or reduction to practice, and in any event upon the request of Isis, of any

Inventions or KIT Methods conceived, created, discovered, developed or reduced to practice by KIT or any of its employees, consultants or agents arising or resulting from performing under this Agreement or any PCD Program and (b) disclose to Isis, on at least an annual basis, or promptly following Isis' earlier written request, the progress of all Studies and all Program Data.

9.4 Pre-Clinical Development License. KIT hereby grants to Isis a non-exclusive, fully paid, royalty-free, license under KIT's rights in KIT Methods for Isis' use.

10. CONFIDENTIAL INFORMATION; PUBLICATION

10.1. Ownership. All rights to Confidential Information will be and remain the property of Isis.

10.2. Obligations. KIT will (a) hold the Confidential Information in strict confidence and take all reasonable precautions to protect the Confidential Information, (b) not divulge the Confidential Information to any third person, including any affiliated entity, without Isis' written consent, and (c) not make any use of the Confidential Information (other than to perform Pre-Clinical Development). Any employees, consultants and agents of KIT given access to any Confidential Information must have a "need to know" and will be bound in writing to restrictions no less restrictive than those set forth in this Section 10.2. KIT will be responsible to Isis for any violations of this Section 10.2 by such individuals/entities.

10.3. Return. After the expiration or earlier termination of this Agreement, a particular PCD Program, or upon the written request of Isis, KIT will turn over to Isis all Confidential Information and all documents or media containing Confidential Information (including all Program Data).

10.4. Authorized Disclosure. If KIT is required to disclose Confidential Information to comply with an applicable law, regulation, legal process, or court order of a government authority, KIT may disclose such Confidential Information only to the person required to receive such disclosure; *provided, however*, that KIT will (a) to the extent permitted by such law, regulation, process, order or rules, first have given prompt (but in no event less than five (5) business days) advance notice to Isis to enable it to seek any available exemptions from or limitations on such disclosure requirement and will reasonably cooperate in such efforts by Isis, (b) furnish only the portion of the Confidential Information which is legally required; (c) use all reasonable efforts to secure confidential protection of such Confidential Information, and (d) continue to perform its obligations of confidentiality set out herein.

10.5. Use of Name. Unless required by law, rule or regulation, neither Isis nor KIT will be permitted to use the name of the other Party in any news or publicity release or other commercial fashion without the prior written consent of the other party; *provided, however*, that Isis will be permitted to use, and KIT hereby grants prior approval for Isis to use, the name of KIT in connection with disclosure of the data and results of a Study. Nothing in this Section 10.5 will be construed as prohibiting Isis from submitting reports with respect to a Study to any Ethics Committee or Regulatory Authority. For purposes of clarification, KIT acknowledges that Isis may be required under federal and state securities laws to disclose the existence and certain basic terms of this Agreement and certain PCD Programs.

10.6. Publication.

10.6.1. KIT may publish Program Data if (i) KIT proposes a publication containing Program Data and Isis consents in writing to such proposed publication, or (ii) Isis notifies KIT that Isis does not intend to publish certain Program Data and such Program Data is published by KIT in

accordance with the terms of this Article 10.6. Further, Isis and KIT agree that publications of Program Data will be produced in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Guidelines.

10.6.2. A copy of any proposed KIT publication or presentation materials, including manuscripts, slides, overheads, outlines, summaries, abstracts or posters will be provided to Isis for Isis' written review and comment at least 30 days prior to the scheduled presentation or publication submission date. If Isis informs KIT within such 30 day time period that postponement of KIT's publication or presentation is necessary in order to protect Isis' patent or other proprietary rights, KIT will postpone such publication or presentation, but KIT will not be required to do so for a period of longer than 3 months.

10.6.3. Notwithstanding the foregoing, Isis will have the absolute right to demand deletion of any Confidential Information (except Program Data) and KIT will delete such information upon written notice from Isis. However, Isis will not request deletions that will preclude the meaningful publication of the Program Data in accordance with CONSORT Guidelines.

11. INDEMNIFICATION

11.1 Indemnification by KIT. KIT will indemnify and hold harmless Isis from any and all liability, loss (including reasonable attorneys' fees) or damage it may suffer (including as a result of claims, demands, costs or judgments against it) that arise or are alleged to arise out of (a) the negligence or willful misconduct of KIT or any of its employees, consultants or agents, (b) the failure of KIT or any of its employees, consultants or agents to comply with Isis' written instructions, (c) KIT's handling, storage or disposal of Materials, or (d) the material breach of this Agreement or any PCD Program by KIT or any of its employees, consultants or agents (including premature cancellation or termination of Pre-Clinical Development).

11.2 Indemnification by Isis. Isis will indemnify and hold harmless KIT from any and all liability, loss (including reasonable attorneys' fees) or damage it may suffer (including as a result of claims, demands, costs or judgments against it) that arise or are alleged to arise out of Isis' clinical or commercial use of Program Data, except to the extent KIT has an obligation to indemnify Isis under Section 11.1 above.

11.3 Conditions. Each Party's agreement to indemnify and hold the other harmless is conditioned upon the indemnified Party (i) providing written notice to the indemnifying Party of any claim, demand or action arising out of the indemnified activities within thirty (30) days after the indemnified Party

has knowledge of such claim, demand or action, (ii) permitting the indemnifying Party to assume full responsibility to investigate, prepare for and defend against any such claim or demand, (iii) assisting the indemnifying Party, at the indemnifying Party's reasonable expense, in the investigation of, preparation of and defense of any such claim or demand; and (iv) not compromising or settling such claim or demand without the indemnifying Party's prior written consent.

12. TERM AND TERMINATION

12.1. Term. This Agreement will be effective on the Effective Date and continue in full force and effect until the date that is three (3) years after the Effective Date. In the event this Agreement expires or is earlier terminated and the term of any PCD Program(s) extends beyond the term of this Agreement (and such PCD Program is not also specifically terminated), this Agreement will continue until expiration or earlier termination of each such PCD Program.

12.2. Termination of Study. Any PCD Program or particular Study under a PCD Program may be terminated by Isis, without cause, upon 30 days written notice.

12.3. Termination for Cause. Any PCD Program or particular Study under a PCD Program may be terminated by either Party, upon 30 days written notice to the other Party, in the event of a material breach of this Agreement or such PCD Program by a Party or any of its employees, consultants and/or agents and such breach is not cured within such 30 day notice period. Notwithstanding the foregoing, in the event a Party disputes that it is in material breach of this Agreement, subject to such 30-day period, the dispute will be referred to the attention of the President of KIT and an Executive Vice President of Isis (the "Executive Officers"). The Executive Officers will meet as soon as reasonably possible thereafter and in good faith attempt to resolve such dispute and attempt to resolve the underlying breach. If, within 30 days after such matter is referred to them, the Executive Officers are unable to resolve such dispute or resolve the underlying breach then, the dispute regarding whether there has been a material breach of the Agreement will referred for resolution by arbitration pursuant to Section 13.7 below. If the arbitrator(s) determines that the Agreement has been materially breached and the breaching Party fails to cure such breach within 30 days of such determination, the non-breaching Party will thereafter be entitled to terminate this Agreement without further delay and pursue any rights and remedies available to such Party (at law or in equity).

12.4. Return of Program Data. In the event of termination of a PCD Program or a particular Study under a PCD Program, KIT will promptly deliver all Program Data, Materials, and other Confidential Information as further described in the applicable PCD Program.

12.5. Survival. Expiration or termination of this Agreement or any PCD Program by either party for any reason will not affect the rights and obligations of the Parties accrued up to such expiration or the effective time of such termination. In addition, the rights and duties under Sections 3.1, 3.4, 3.5, 3.6, 4, 5, 7, 8, 9, 10, 11, 12 and 13 will survive the expiration or termination of this Agreement.

13. GENERAL PROVISIONS

13.1. Notice. All notices required or permitted under this Agreement and any PCD Program will be in writing and will be deemed effectively given: (a) upon personal delivery to the Party to be notified, (b) when sent by confirmed facsimile or email if sent during the normal business hours of the recipient (if not sent during such hours, then on the next business day), (c) 5 days after timely deposit as registered or certified mail, return receipt requested, postage prepaid or (d) 2 days after timely deposit with an internationally recognized overnight courier, specifying next day delivery, with written verification of receipt. All notices will be sent to the appropriate address(es) or number(s) of the Party to be notified as set forth below, or at such other address(es), number(s) or person(s) as such Party may designate by advance written notice to the party providing notice:

If to KIT:

Korea Institute of Toxicology
100 Jangdong
Yuseong, Daejeon
305-343, Korea
Attention: Sang Seop Han, DVM, Ph.D.
President

and a copy to each individual designated in a PCD Program as to receive notice.

If to Isis:

1896 Rutherford Road
Carlsbad, CA 92008
Fax: 760-268-5035
Attn: Executive Vice President & CFO

with a copy to:

1896 Rutherford Road
Carlsbad, CA 92008
Fax: 760-268-4922
Attn: Vice President, Legal

and a copy to each individual designated in a PCD Program as to receive notice.

13.2. Independent Contractor. KIT will perform Pre-Clinical Development as an independent contractor and will have complete and exclusive control over KIT's employees, consultants and agents. Notwithstanding the collaborative relationship created by this Agreement, nothing herein will preclude Isis from seeking and/or entering into a separate relationship with a third-party for the provision of pre-clinical research of a same or similar nature as the Pre-Clinical Development.

13.3. Entire Agreement. This Agreement (including the PCD Plan and any PCD Programs) constitutes the entire understanding between the Parties with respect to the subject matter covered hereby and supersedes any prior negotiations, representations, agreements and understandings regarding such subject matter. In the event there is a conflict between the terms and conditions of this Agreement, and the terms and conditions of any PCD Program, the terms and conditions of this Agreement will govern and control (unless expressly stated otherwise in the PCD Program).

13.4. Modifications; Waivers. Neither this Agreement nor any PCD Program may be amended, supplemented or otherwise modified except by an instrument in writing signed by each of the Parties. The failure of any Party to insist upon strict performance of any provision of this Agreement or any PCD Program or to exercise any right hereunder or thereunder will not constitute a waiver of that provision of or right under this Agreement or such PCD Program or of any other provision of or right under this Agreement or such PCD Program.

13.5. Severability. If any provision of this Agreement or any PCD Program is declared invalid, illegal or unenforceable, such provision will be severed and all remaining provisions will continue in full force and effect.

13.6. Governing Law. This Agreement and each PCD Program will be construed and enforced in accordance with the laws of England, without regard to its choice of law principles.

13.7. Dispute Resolution.

13.7.1. Any dispute that arises under this Agreement will be first referred to the Executive Officers for resolution as set forth in Section 12.3 above. In the event that the Executive Officers fail to resolve the dispute, the Parties agree to refer the dispute to arbitration.

13.7.2. Arbitration Proceedings. If the Parties pursue arbitration proceedings under Section 12.3 or 13.7.1 above, the dispute will be finally settled under the Rules of Conciliation and Arbitration of the International Chamber of Commerce by one or more arbitrators appointed in accordance with the rules. Such arbitration will be carried out in Geneva, Switzerland. The language to be used in the arbitration proceeding shall be English.. Either Party may apply to the arbitrator(s) or to a court for interim injunctive relief until the arbitration decision is rendered or the dispute, controversy or claim is otherwise resolved.

13.7.3. Costs and Expenses. Each Party will bear its own costs and expenses and attorneys' fees and an equal share of the arbitrator's fees and any administrative fees of arbitration. Notwithstanding the foregoing, if a Party has been found to be in material breach of this Agreement, the breaching Party will be responsible for all the costs and expenses of the arbitrator and any administrative fees of arbitration.

13.7.4. Confidentiality. Except to the extent required by law, neither a Party nor the arbitrator may disclose the existence, content, or results of a arbitration without the prior written consent of both Parties, and provided that the foregoing will not prevent a Party from confidentially disclosing the existence, content and results of the arbitration in confidence to its directors, professional advisors, and existing or potential investors or acquirers, and others on a need to know basis or as required by law or regulation.

13.8. Due Authorization; Authority; Conflicts. The persons executing this Agreement represent and warrant that they have full power and authority to enter into this Agreement on behalf of the entities they purport to represent. Each Party represents and warrants to the other Party as of the Effective Date and the effective date of each PCD Program that this Agreement and such PCD Program has been duly authorized, executed and delivered and that the performance of its obligations under this Agreement and such PCD Program does not conflict with any order, law or regulation or any agreement or understanding by which such party or its assets or property are bound and that no such agreement or understanding would prevent it from fulfilling its obligations under this Agreement or such PCD Program and that, during the term of this Agreement and such PCD Program, it will not enter into any agreement that would materially impair its ability to fulfill its obligations under this Agreement or such PCD Program.

13.9. Assignment. KIT will have no right to assign, subcontract, transfer, or otherwise dispose of its rights under this Agreement or any PCD Program or to assign the burdens hereof or thereof without the prior written consent of Isis. Subject to the foregoing, this Agreement and any PCD Program will inure to the benefit of and be binding upon the Parties' successors and assigns.

13.10. Conflicts. In the event of a conflict between this Agreement and any PCD Program, the terms of this Agreement will govern and control, unless such PCD Program specifically references the conflicting provision in this Agreement and states that such provision of this Agreement is superseded by the relevant provision of such PCD Program.

13.11. Remedies. Isis' rights and remedies hereunder (including those set forth in Section 12) are cumulative and not exclusive of any rights or remedies that are otherwise available under law.

13.12. Attorneys' Fees. Subject to Section 13.7 above, if any action at law or in equity is necessary to enforce or interpret the terms of this Agreement or any PCD Program, the prevailing Party will be entitled to reasonable attorneys' fees, costs and disbursements, in addition to any other relief to which such Party may be entitled. In addition, if any action is properly instituted to collect on any amount due under any PCD Program, the Party against whom the collection is instituted will pay the reasonable costs and expenses incurred in connection with such action.

14. FORCE MAJEURE

14.1. The Parties are not liable for the failure to perform their obligations under the present Agreement, if such failure is caused by acts of God such as fire, flood, or earthquake, provided that these circumstances have directly affected the performances of the present Agreement. In this case, the time obligation of performances can be extended for a period to compensate for the duration of such circumstances.

14.2. The Party which cannot perform its obligations under the present Agreement shall notify the other Party by email or fax no later than fifteen days after the beginning of such causes.

14.3. If these circumstances last longer than six months, either Party shall be entitled to terminate the entire Agreement.

IN WITNESS WHEREOF, the Parties have executed this Agreement in duplicate originals effective as of the Effective Date.

ISIS PHARMACEUTICALS, INC.	**KOREA INSTITUTE OF TOXICOLOGY**
By: */s/ Stanley T. Crooke, MD, PhD*	By: */s/ Sang Seop Han*
Name: Stanley T. Crooke, MD, PhD	Name: Sang Seop Han
Title: Chairman & CEO	Title: President

Exhibit A

"Affiliates" means, with respect to the Party specified, any individual or entity that directly or indirectly controls, is controlled by or is under common control with such Party.

"C.F.R." means the U.S. Code of Federal Regulations.

"Confidential Information" means Program Data, bioanalytical methods, the existence of this Agreement and its terms, and all information disclosed (whether orally, electronically, or in writing) to KIT by Isis and/or Isis' employees, consultants or agents or acquired by KIT in the course of providing Pre-Clinical Development (whether before or after the Effective Date); *provided*, *however*, that "Confidential Information" will not include any information KIT can document by written records (a) is or (through no improper action or inaction by the KIT or any of its employees, consultants or agents) becomes generally available or known to the public, (b) was known to KIT on a non-confidential basis prior to receipt from Isis or (c) was rightfully disclosed to KIT by a third party having no obligation of confidentiality.

"Ethics Committee" means any board, committee or other group designated to review biomedical research involving humans or animals as subjects and monitoring or having authority over a Study.

"Identified Employee" means an English-speaking KIT employee proposed by KIT and approved by Isis to perform Pre-Clinical Development in accordance with one or more PCD Programs.

"IND" means an investigational new drug application, as defined in 21 C.F.R. 312 or any successor regulation or any equivalent application or filing outside the United States to seek such regulatory approval from a Regulatory Authority in such jurisdiction.

"Inventions" means any and all ideas, concepts, inventions, discoveries, techniques, processes, machines, manufactures, methods, developments, improvements, designs, systems, specifications, schematics, drawings, information, protocols, devices (including prototypes), works of authorship, formulae, algorithms, computer programs, trade secrets, technology, know-how, evaluations, studies, analytical results, assays, data, specifications, technical information, and samples, whether or not patentable.

"Intellectual Property Rights" means all intellectual property rights worldwide arising under statutory or common law or by contract and whether or not perfected, now existing or hereafter filed, issued, or acquired including all (i) United States and foreign patent applications containing one or more claims, (ii) United States provisional applications, (iii) non-provisional, continuation, continuation-in-part, and divisional applications that claim the priority of any patent rights described in (i) or (ii) above, and (iv) United States and foreign patents issuing on patent rights described in (i) and (iii) above and reissues, reexaminations, and extensions thereof; rights relating to the protection of trade secrets and confidential information; and any right analogous to those set forth herein and any other proprietary rights relating to intangible property.

"KIT Methods" means (i) any methods, techniques, or procedures related to the conduct of toxicological studies that are conceived, created, discovered or developed by KIT in performance of the Pre-Clinical Development, and (ii) any improvements or modifications made by KIT to Isis' bioanalytical methods as contemplated by Section 3.1 above.

"Level 1 Development" has the meaning set forth in Section 2.1 above.

"Level 1 Development Studies" include all of the following:

- [***]
- [***]
- [***]

- [***]
- [***]
- [***]
- [***]
- [***]

"NDA" means a new drug application submitted to the United States Food and Drug Administration, or any successor application or procedure, or any equivalent application or filing outside the United States to seek regulatory approval from a Regulatory Authority in such jurisdiction.

"Net Sales" means the definition of "Net Sales" (or similar term) set forth in a bona fide separate written agreement between Isis and a third-party related to the commercialization of the applicable Product(s) for which royalties are being calculated under this Agreement. In the event no such agreement exists between Isis and a third-party net sales has the meaning set forth in Exhibit D.

"Party" means either Isis or KIT, as the case may be, and "Parties" means both Isis and KIT.

"PCD Plan" has the meaning set forth in Section 2.2 above.

"PCD Program" has the meaning set forth in Section 2.3 above.

"Pre-Clinical Development" means Level 1 Development performed under a PCD Program.

"Product(s)" means an Isis drug product (containing a Study Drug) approved for marketing by a Regulatory Authority, where data resulting from Pre-Clinical Development was a part of the applicable IND or NDA submission for such drug product.

"Program" means a development project involving the conduct of one or more Studies.

"Program Data" has the meaning set forth in Section 9.2 above.

"Protocol" means a written document drafted by KIT that sets forth the specific manner in which a particular Study will be performed.

"Regulatory Authority" means any public or private entity or agency monitoring or having authority over a Study (and includes the U.S. Food and Drug Administration).

"Study" or "Studies" means experiment(s) or investigation(s) performed by KIT pursuant to a Protocol.

"U.S." means the United States of America.

"U.S.C." means the United States Code.

Exhibit B

PCD PLAN

Background

Isis designs and develops drugs and would like to collaborate in the performance of certain pre-clinical research experiments in which its drugs are analyzed *in vitro* and/or administered to animal subjects, the results of which are intended to be submitted to or held for inspection by a Regulatory Authority. KIT has substantial experience and expertise in supporting and conducting Pre-Clinical Development, and therefore, the Parties wish to collaborate in order to utilize their respective expertise. This PCD Plan embodies the particular guiding principles by which the Parties will collaborate under the Agreement and perform Pre-Clinical Development under PCD Programs.

Isis' Responsibilities

Isis' responsibilities under this collaboration with KIT are to:

- [***]
- [***]
- [***]
- [***]
- [***]
- [***]
- [***]
- [***]

KIT Responsibilities

KIT's responsibilities are to conduct, in collaboration with Isis, certain of the following Level 1 Development Studies as specified by Isis in the applicable PCD Program:

- [***]
- [***]

- [***]
- [***]
- [***]
- [***]
- [***]
- [***]
- [***]

Implementation

PCD Program. Isis will work closely with KIT to formulate a PCD Program for the conduct of all Studies, enabling KIT to produce a responsive Protocol(s) for each Study. Protocol(s) will be finalized and agreed upon in writing by both Parties and attached to the PCD Program as a part thereof.

For identification purposes, each PCD Program will be assigned a unique number and reference the underlying Studies by each Protocol title or other reasonable means. It is contemplated that one PCD Program will be entered into for each Study Drug and that each PCD Program will, among other things, set forth in detail:

(a) the specific Pre-Clinical Development to be performed and the form and substance of deliverables to be provided by KIT under the PCD Program with respect to each Study (which Pre-Clinical Development and deliverables will be defined in a reasonably objective manner such that their respective occurrences are readily verifiable);

(b) the period during or by which the Pre-Clinical Development will be performed or such deliverable will be provided;

(c) the location or locations at which the Pre-Clinical Development will be performed;

(d) the price to be paid by Isis for performance of the Pre-Clinical Development (including the effect of failure to meet any specified timeline or to provide adequate Pre-Clinical Development), which expenses/fees incurred by KIT are reimbursable by Isis, if any, and when such payment and/or reimbursement, if any, will be due (which points will be defined in a reasonably objective manner such that their respective occurrences are readily verifiable); and

(e) additional representations and collaboration obligations of the Parties and requirements imposed on the Parties applicable to providing such Pre-Clinical Development.

Changes. KIT and Isis acknowledge that, from time to time after execution of a PCD Program, changes/additions to the PCD Program may be requested (including with respect to the items covered in items (a) through (e) above) (each, a "Change Order"). Any Change Order will be negotiated in good faith. In the event KIT reasonably determines that a Change Order is reasonably likely, KIT will promptly notify Isis.

Compliance. In connection with any PCD Program, KIT will inform Isis of obligations and requirements (both affirmative and negative) imposed upon or with which Isis must comply in connection with such Program (including any shipping, labeling or import/export requirements associated with each Study).

Exhibit C

Form of PCD Program

PCD PROGRAM # [ ]

DRUG NAME:	ISIS [ ]
PROTOCOL NO(S):	[ ]
DATE:	[ ]

This PCD Program [ ] ("PCD Program") is made and entered into as of [ ] by and between **Isis Pharmaceuticals, Inc.** ("Isis"), and **Korea Institute of Toxicology** ("KIT").

WHEREAS, Isis and KIT have entered into that certain Pre-Clinical Development Collaboration Agreement dated March 23, 2007 (the "Agreement"); and

WHEREAS, pursuant to the Agreement, KIT and Isis have agreed that KIT will conduct certain Pre-Clinical Development in accordance with PCD Program(s), and Isis and KIT now desire to enter into this PCD Program.

WHEREAS, KIT and Isis specifically desire that KIT conduct certain Level 1 Development with respect to [ ] (the "Program") involving one or more Studies of the drug, ISIS [ ] ("Study Drug") as set out in the Protocol(s) to be agreed upon by the Parties.

NOW, THEREFORE, in consideration of the mutual covenants contained herein, the Parties hereby agree as follows:

1. Defined Terms. When used in this PCD Program, capitalized terms not otherwise defined in this PCD Program will have the meanings ascribed to them in the Agreement.

2. Protocol. The Studies will be conducted as detailed in each Protocol (which KIT will produce) which, when finalized and agreed to by the Parties, will be incorporated herein by reference and will be considered an integral part of this PCD Program.

3. Scope of Pre-Clinical Development; Deliverables. KIT will perform the following Studies in accordance with the attached Study Protocol(s), the Agreement, and the PCD Plan:

- **[NOTE: INSERT HERE ALL STUDIES TO BE PERFORMED BY KIT FOR THIS PCD PROGRAM]**

KIT also agrees to prepare written reports in a form and with substance sufficient to support Isis' IND and/or NDA registration to a Regulatory Authority, and provide such reports (including all Program Data) to Isis within 30 days following the completion of each Study.

4. Royalty Rate. The royalty rate payable to KIT, in accordance with and subject to the terms of the Agreement, [***] is [***]%.

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5. Time-line. The Pre-Clinical Development under this PCD Program will be performed in accordance with the timeline agreed upon by both Parties in each Protocol.

6. Budget and Payment Schedule. Isis agrees to provide Isis Funding in support of the Pre-Clinical Development under this PCD Program, in accordance with Section 6.1 of the Agreement. Other than Isis Funding and reimbursement by Isis for agreed upon costs and expenses set forth in this PCD Program, KIT will pay any costs required to conduct the Pre-Clinical Development under this PCD Program.

7. Costs and Expenses. Isis will pay [***] shipping costs related to shipment of Study Drug, and will reimburse KIT for [***] of the actual cost of the [***] (or $[***] per [***], whichever is [***]) within thirty (30) days of the first dose of Study Drug in the monkeys pursuant to the Protocol(s), and Isis' receipt of an invoice. When invoicing Isis under this PCD Program for payment and reimbursement, KIT agrees to provide Isis with copies of all documentation related to such reimbursable costs and expenses.

8. Study Drug. Isis agrees to provide KIT with sufficient Study Drug for the purpose of KIT's performance of Pre-Clinical Development under this PCD Program, and Study Drug will be considered Materials in accordance with the Agreement.

9. Changes and Modifications. Any changes requested in this PCD Program after Isis agrees to and signs this PCD Program will require a written Change Order in accordance with the Agreement. When written approval of the Change Order is received from Isis the change will be made.

10. Term and Termination; Transition Process. (a) The term of this PCD Program will commence upon execution of this PCD Program by KIT and Isis and will continue until completion of the Pre-Clinical Development hereunder, *provided, however*, either party may terminate this PCD Program in accordance with Article 12, Term and Termination, of the Agreement.

(b) If this PCD Program is so terminated, or KIT is otherwise unable or unwilling to complete the Pre-Clinical Development under this PCD Program (which KIT understands will significantly harm Isis), KIT agrees to (i) promptly notify Isis that performance of the Pre-Clinical Development has or will cease, (ii) work cooperatively with Isis to properly wind down and conclude all Study activities in a manner that is designed to preserve the integrity of the Program Data, (iii) transfer to Isis all Program Data in KIT's possession and any other information Isis deems necessary or useful to enable continuation of the Studies, and (iv) agree with Isis on an [***] other than the [***] previously agreed to by the Parties, that fairly and equitably compensates KIT based upon the [***] actually completed by KIT under this PCD Program.

11. Incorporation by Reference; Conflict. The provisions of the Agreement are hereby expressly incorporated by reference into and made a part of this PCD Program. In the event of a conflict between the terms and conditions of this PCD Program and those of the Agreement, the terms of the Agreement will take precedence and control.

IN WITNESS WHEREOF, the parties have hereunto signed this PCD Program effective as of the day and year first written above.

Signed For And On Behalf Of	Signed For And On Behalf Of
Korea Institute of Toxicology	**Isis Pharmaceuticals, Inc.**
By: _____	By: _____
Name: _____	Name: _____
Title: _____	Title: _____
Date: _____	Date: _____

Exhibit D

Royalty Provisions Applicable to Section 7.2 (b) of the Agreement

With respect to Product(s) that Isis is commercializing on its own and not pursuant to a bona fide commercialization agreement with a third-party, Isis' obligation to pay royalties to KIT on Net Sales of Isis Product(s) under Section 7.1 of the Agreement, will (on a country-by-country basis) begin upon the first

commercial sale of such Product(s) by Isis and will continue so long as there is a valid claim on an issued patent owned by Isis that covers the use or sale of such Product in such country. The specific aspects of royalty payment timing, payment method, currency, records retention, audit rights, and other material commercial terms customarily applicable to royalties will be handled in the following manner:

Timing of Royalty Payments. Any royalties due pursuant to Section 7.2(b) will be paid within 45 days of the end of each calendar quarter and will be calculated in respect of the Net Sales occurring in such calendar quarter.

Currency; Payment Method. Any royalties due to KIT will be paid in U.S. dollars, by wire transfer in immediately available funds to an account designated by KIT.

Records Retention. Isis will maintain complete and accurate books, records and accounts that fairly reflect Net Sales with respect to each Product, in each case in sufficient detail to confirm the accuracy of any payments required hereunder and in accordance with GAAP, which books, records and accounts will be retained by Isis for a period of 5 years after the end of the period to which such books, records and accounts pertain.

Audit Rights. KIT will have the right to have an independent certified public accounting firm of nationally recognized standing, reasonably acceptable to Isis, have access during normal business hours, and upon reasonable prior written notice, to Isis' records as may be reasonably necessary to verify the accuracy of Net Sales for any calendar quarter or calendar year ending not more than 24 months prior to the date of such request; *provided, however*, that KIT will not have the right to conduct more than one such audit in any calendar year. KIT will bear the cost of such audit unless the audit reveals an underpayment of more than 5% from the reported results, in which case Isis will bear the cost of the audit.

Net Sales. For purposes of this Exhibit D, "*Net Sales*" means the gross receipts received by Isis for the sale of a Product to a third party by Isis, less deductions for (i) prompt payment or other trade and quantity discounts actually granted, (ii) amounts paid or credited for returns or allowances, (iii) the amount of any sales tax or other taxes assessed directly on the sale of such Product which is not refunded, (iv) charge back payments or rebates granted to managed health care organizations or federal, state and local governments, their agencies, purchasers and reimbursers, and (v) transportation and delivery charges, including insurance premiums actually incurred.

Notwithstanding the foregoing, amounts received by Isis or its Affiliates or sublicensees for the sale of Products among Isis, its Affiliates or sublicensees whether for their internal use or for resale or other disposition with not be included in the computation of Net Sales hereunder. For purposes of this Exhibit D, a distributor will not be deemed a sublicensee and sales by Isis, its Affiliates or sublicensees to a distributor will not be subject to royalties.

EXHIBIT 10.41

EXECUTION VERSION

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

STOCK PURCHASE AGREEMENT

by and among

IBIS BIOSCIENCES, INC.,

ISIS PHARMACEUTICALS, INC.

and

ABBOTT MOLECULAR INC.

Dated:

December 17, 2008

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STOCK PURCHASE AGREEMENT

THIS STOCK PURCHASE AGREEMENT (this "Agreement") is made and entered into as of the 17th day of December, 2008, by and among Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis"), Ibis Biosciences, Inc., a Delaware corporation and Affiliate of Isis ("Ibis"), and Abbott Molecular Inc., a Delaware corporation ("AMI") and Affiliate of Abbott Laboratories, an Illinois corporation ("Abbott"). AMI, Ibis and Isis are sometimes referred to herein individually as a "Party" and collectively as the "Parties."

WHEREAS, on January 30, 2008, the Parties entered into the Master Agreement, a Call Option Agreement and the Investor Rights Agreement, pursuant to which, among other things, AMI acquired the Shares, the option, exercisable in AMI's sole discretion, to purchase the Additional Shares from Ibis and the Call Option, for an aggregate purchase price of $20,000,000;

WHEREAS, as of June 27, 2008, the Parties entered into a Stock Subscription Agreement, pursuant to which, among other things, AMI acquired the Additional Shares for an aggregate purchase price of $20,000,000;

WHEREAS, Isis owns 1,000,000 shares of Ibis' Common Stock (the "Remaining Shares");

WHEREAS, on December 12, 2008, pursuant to the terms of the Call Option Agreement, AMI exercised the Call Option, electing to acquire the Remaining Shares pursuant to the terms hereof; and

WHEREAS, subject to the terms and conditions set forth in this Agreement, Isis desires to sell to AMI and AMI desires to acquire from Isis the Remaining Shares.

NOW, THEREFORE, in consideration of the mutual promises, representations, warranties, and covenants hereinafter set forth and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

Section 1. DEFINITIONS. Capitalized terms used and not otherwise defined herein have the meanings ascribed to such terms in this Section 1.

(a) "Abbott Transaction Team" means the individuals listed on Schedule 1(a).

(b) "Additional Shares" means 114,250 shares of Common Stock acquired by AMI pursuant to the Stock Subscription Agreement, as may be held from time to time by AMI and its permitted assigns, which, together with the Shares, represent approximately 18.6% of the issued and outstanding Common Stock.

(c) "Affiliate" of an entity means any other entity that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such first entity. For purposes of this definition only, "control" (and, with correlative meanings, the terms "controlled by" and "under common control with") means the

possession, directly or indirectly, of the power to direct the management or policies of an entity, whether through the ownership of voting securities or by Contract relating to voting rights or corporate governance; *provided*, that, with respect to Isis, the term "Affiliate" shall specifically exclude [***].

(d) "Applicable Law" or "Law" means all applicable common law, laws, constitutional provisions, ordinances, statutes, rules, regulations, administrative rulings, executive orders and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including but not limited to any applicable rules, regulations, guidelines, or other requirements of Governmental Authorities that may be in effect from time to time.

(e) "Applicable Rate" means as of any particular date, the prime rate as quoted in the Money Rates Section of *The Wall Street Journal*, plus [***]%.

(f) [***]

(g) "Bonus Arrangement" means the Special Bonus Opportunity communicated to Ibis employees, pursuant to which a bonus pool of [***] will be payable by Ibis to Ibis Employees in the event the Closing is consummated.

(h) "Business" means researching, developing, manufacturing, selling, marketing, distributing and using a system, process or reagents for the identification and/or quantitation of nucleic acids or the performance of services relating to any of the foregoing, as conducted by Ibis or by Isis, with respect to the Division, on and prior to the Closing Date.

(i) "Business Day" means any day other than a Saturday, Sunday, or a day on which the banks in Chicago, Illinois are authorized or obligated by Law to close.

(j) "Call Option" has the meaning ascribed to such term in the Call Option Agreement.

(k) "Call Option Agreement" means that certain Amended and Restated Call Option Agreement, dated as of November 18, 2008, by and among Isis, Ibis and AMI.

(l) "Capital Stock" means all capital stock, equity or controlling interests and other securities in an issuer, including, without limitation, options, warrants, depositary receipts, stock appreciation or phantom stock rights or other agreements or undertakings, including stock or securities convertible or exchangeable for any shares of capital stock, equity or controlling interests or other securities in an issuer or containing any profit participation features or pursuant to which such issuer is or could be bound to issue or repurchase any capital stock, equity or controlling interests or other securities.

(m) "Change of Control" means, with respect to any Person, the occurrence of (i) any consolidation or merger of such Person with or into any other Person, or any other corporate reorganization or transaction (including the acquisition of Capital Stock of such Person (or any rights to acquire, or securities convertible into or exchangeable for, any such

Capital Stock)), whether or not such Person is a party thereto, in which the stockholders or equity-holders of such Person or other Persons controlling such Person immediately prior to such consolidation, merger, reorganization or transaction, own Capital Stock either (A) representing directly, or indirectly through one or more entities, less than fifty percent (50%) of the economic interests in or voting power of such Person or other surviving entity immediately after such consolidation, merger, reorganization or transaction or (B) that does not directly, or indirectly through one or more entities, have the power to elect a majority of the entire board of directors or equivalent governing body of such Person or other surviving entity immediately after such consolidation, merger, reorganization or transaction or (ii) a sale, lease, license or other disposition of all or a material portion of the assets of such Person.

(n) "Claim" means any claim, lawsuit, demand, audit, investigation, charge, suit, hearing, notice of a violation, litigation, action, proceeding, order, judgment, grievance, or arbitration, whether civil, criminal, administrative or otherwise, whether at law or in equity, or any inquiry likely to result in any of the foregoing.

(o) "Code" means the Internal Revenue Code of 1986, as amended from time to time.

(p) "Common Stock" means the Common Stock of Ibis, par value $0.001 per share.

(q) "Confidential Information" means all information and any tangible embodiments thereof provided by or on behalf of the Disclosing Party to the Receiving Party or to the Receiving Party's Representatives either in connection with the discussions and negotiations pertaining to the Transaction Documents or in the course of performing the Transaction Documents, including without limitation: know-how; data; knowledge; practices; processes; research and development plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the Disclosing Party or to its present or future products, sales, suppliers, customers, employees, consultants, independent contractors, investors or business; regardless of whether any of the foregoing are marked "confidential" or "proprietary" or communicated to the other by the Disclosing Party in oral, written, graphic or electronic form. Notwithstanding the foregoing, information of a Party will not be deemed Confidential Information to the extent that the Receiving Party can show by competent proof that such information:

(i) is or becomes generally available to the public other than as a result of an unauthorized disclosure by the Receiving Party or its Representatives;

(ii) was available to the Receiving Party or its Representatives on a non-confidential basis prior to its disclosure by the Disclosing Party or its Representatives;

(iii) is or becomes available to the Receiving Party or its Representatives from a Person, other than the Disclosing Party or its Representatives,

who is not bound by a confidentiality obligation to the Disclosing Party or its Representatives; or

(iv) is independently developed by the Receiving Party or its Representatives without reference to or use of any Confidential Information of the Disclosing Party.

(r) "Contract" means any contract, lease, deed, mortgage, license, instrument, note, commitment, undertaking, understanding, indenture, joint venture, purchase order, service order and all other agreements and arrangements, whether oral or written.

(s) "Contribution Agreement" means the Contribution Agreement, dated as of July 31, 2007, by and between Isis and Ibis.

(t) "Corporate Services Agreement" means that certain Corporate Services Agreement, dated as of July 31, 2007, by and between Isis and Ibis.

(u) [***]

(v) "Division" means the Ibis Biosciences division of Isis.

(w) "Earnout Threshold" means $140 million minus all commercial revenue for the period beginning on [***], as set forth on Exhibit B, which has been prepared in accordance with GAAP and Isis' internal controls and procedures for financial reporting and delivered pursuant to Section 8.17.

(x) "Employee Pension Benefit Plan" has the meaning set forth in Section 3(2) of ERISA.

(y) "Employee Welfare Benefit Plan" has the meaning set forth in Section 3(1) of ERISA.

(z) "Encumbrance" means any mortgage, covenant, hypothecation, condition, Claim, easement, encroachment, right of way, restriction, option, lien (statutory or otherwise), pledge, charge, license, security interest or encumbrance of any nature whatsoever.

(aa) "Environmental Laws" means any federal, state, local or foreign statutes, ordinances, codes, treaties, or other Laws (including, without limitation, the Comprehensive Environmental Response, Compensation, and Liability Act, the Resource Conservation and Recovery Act, the Clean Air Act, the Clean Water Act, the Toxic Substances Control Act, the Oil Pollution Prevention Act, the Federal Insecticide, Fungicide, & Rodenticide Act, the Safe Drinking Water Act, the Hazardous Materials Transportation Act, the Solid Waste Disposal Act, the Emergency Planning and Community Right-to-Know Act, the Occupational Safety and Health Act), including any regulations, rules, plans, other criteria, policies or guidelines promulgated pursuant to such Laws, and all common law, orders, judgments, decrees, judicial or agency interpretations now or hereafter in effect relating to pollution, the generation, production, installation, use, storage, treatment, transportation, Release, threatened Release, investigation, monitoring, remediation, cleanup, abatement, removal, or disposal of Hazardous

Materials, noise control, odor or the protection of public or workplace health or safety, natural resources, or the environment.

(bb) "ERISA" means the Employee Retirement Income Security Act of 1974, as amended.

(cc) "Fundamental AMI Representations" means those representations and warranties of AMI set forth in Section 5.2(a) (Power and Authority), Section 5.2(b) (Enforceability), Section 5.2(c) (Governmental Authority; Consents), and Section 5.2(d) (No Conflicts).

(dd) "Fundamental Isis Representations" means those representations and warranties of Isis set forth in Sections 5.1(a) (Power and Authority), 5.1(b) (Enforceability), 5.1(c) (Governmental Authority; Consents), 5.1(d) (No Conflicts), 5.2(e) (Due Organization; Qualification), 5.1(g) (Capitalization; Voting Rights), 5.1(j) (Title to Properties and Tangible Assets; Liens, etc.), 5.1(k) (Sufficiency of Assets), 5.1(m) (Compliance with Other Instruments), 5.1(t)(ii) (Certain Balance Sheet Items) and 5.1(v) (Brokers' Fees).

(ee) "GAAP" means United States generally accepted accounting principles, applied on a consistent basis.

(ff) "Governmental Authority" means any governmental or quasi-governmental agency, department, bureau, office, center, institute, court, commission or other unit of the government of the United States of America or of any of its respective States or local units of government thereof, or of a foreign sovereign or of a provincial, regional or metropolitan government thereof, including, without limitation, any Regulatory Authority.

(gg) "[***]" means the [***] identified on Exhibit C, which has been prepared in accordance with GAAP and Isis' internal controls and procedures for financial reporting, as updated and delivered pursuant to Section 8.17.

(hh) "[***]" means any payments due to Ibis from a [***] with respect to [***] awarded to Ibis or Contracts with Ibis, in each case to the extent Ibis has performed the research or other services described in the [***] or Contract, but not received payment therefor prior to the Closing Date.

(ii) "Hazardous Materials" means any substance, chemical, solvent, compound, waste, residue, contaminant or other material which is regulated by or forms the basis of liability now or hereafter under any Environmental Law, including, without limitation: (i) any "solid waste," "dangerous goods," "hazardous waste," "hazardous substance," "hazardous material," "extremely hazardous waste," "pollutant," "contaminant," "hazardous constituent," "special waste," "universal waste," "toxic substance," or any other similar term or phrase as defined under any Environmental Law; (ii) any petroleum, or petroleum products, byproducts or breakdown products, including crude oil and any fraction thereof; (iii) natural synthetic gas usable for fuel; (iv) any asbestos, lead-based paint, polychlorinated biphenyl, mold, radon gas, radioactive material or byproduct, isomer of dioxin, or any material or thing containing or composed of such substance or substances; and (v) any virus, bacteria, protozoa, parasite, fungi, or other pathogen or any other substance, chemical, solvent, compound, waste, residue,

contaminant or other material which is hazardous, toxic, poisonous, reactive, corrosive or otherwise may present a threat to human health, safety, natural resources, wildlife or the environment.

(jj) "Ibis Net Sales" means:

(i) the gross amount billed by Ibis or its Affiliates after the Closing for the sale or other transfer or disposition of Products to, or performance of Services for, non-Affiliate third parties in bona fide arms length transactions, less deductions for:

A. discounts, including cash discounts, customary trade allowances or rebates actually taken, and promotional discounts;

B. credits or allowances given or made for rejection, recall or return of previously sold Products and rebates for previously provided Services;

C. any Tax (including any Tax such as a value added or similar Tax) levied on the sale, transportation or delivery of Products when included on the invoice or other written document between the parties as payable by the purchaser and collectable by Ibis; and

D. freight, postage, transportation, insurance and duties on shipment of Product when included on the invoice or written document between the parties as payable by the purchaser and collectable by Ibis;

(ii) [***]; and

(iii) the amount of any [***].

Ibis Net Sales calculations shall be applied as provided above and modified as appropriate as follows:

1. When a Product is sold or licensed by Ibis or its Affiliates or a Service is provided to a non-Affiliate third party with whom Ibis or such Affiliate does not deal at arms length, Ibis Net Sales for that Product or Service shall equal an average of Ibis Net Sales for similar quantities of Products sold or Services provided within the same calendar quarter in an arms length transaction in the same geographic market and class of purchasers or Service recipients as the non-arms length purchaser or Service recipient.

2. In the event that a Product is sold or a Service provided in combination with any other product(s) or service(s), Ibis Net Sales with respect to the Product or Service of the combination shall be determined by the fraction A over A + B in which "A" is Ibis Net Sales of the Product or Service portion of the combination when sold separately during the applicable calendar quarter, and "B" is Ibis Net Sales of the other product(s) or service(s) of the combination product or service when sold separately during the applicable calendar quarter.

3. In the event a Product or Service is incorporated into a profile in which said Product or Service contributes only a small proportion of the value of the total package, but the adjustment set forth in paragraph 2, above is impractical or if similar quantities of product(s) are not sold or similar quantities of Services are not provided pursuant to paragraph 1, above, then the Parties shall negotiate in good faith to establish an equitable adjustment to Ibis Net Sales for such Product or Service to fairly reflect the proportion of the value of the profile contributed by the Product or Service or the value of the Product or Service.

(kk) "Indebtedness" means (i) all indebtedness or other obligations of Ibis for borrowed money, whether current, short-term or long-term, secured or unsecured, and all accrued interest, premiums, penalties and other obligations relating thereto, (ii) all indebtedness of Ibis for the deferred purchase price of property or services which is not evidenced by accounts payable incurred in the ordinary course of business, (iii) all existing lease obligations of Ibis under leases which are capital leases in accordance with GAAP, (iv) any liability of Ibis under deferred compensation plans, phantom stock plans, severance or bonus plans, or any change in control or similar payment or increased cost which is triggered or made or will be made payable by Ibis as a result of the transactions contemplated hereby, other than the Bonus Arrangement, (v) any off balance sheet financing of Ibis, (vi) any payment obligations of Ibis in respect of banker's acceptances or letters of credit, (vii) any liability of Ibis with respect to interest rate swaps, collars, caps and similar hedging obligations, (viii) all obligations of Ibis arising under or with respect to any conditional sale or other title retention agreement with respect to property acquired by Ibis, (ix) past due or deferred rent of Ibis, (x) the amount of accounts payable owed by Ibis to any Person that have not been paid within 45 days of the date of invoice thereof (xi) all "cut" but "uncashed" checks of Ibis outstanding as of the Closing, (xii) any indebtedness referred to above of any Person which is either guaranteed by, or secured by a security interest upon any property owned by, Ibis and (xiii) accrued and unpaid interest of, and prepayment premiums, penalties or similar contractual charges arising as a result of the discharge of any such foregoing obligation.

(ll) "Intellectual Property" means all of the following in any jurisdiction throughout the world: (i) patents, patent applications and patent disclosures and statutory invention registrations, including reissues, divisions, continuations, continuations in part, extensions and reexaminations thereof; (ii) trademarks, service marks, trade dress, trade names, corporate names, logos and slogans (and all translations, adaptations, derivations and combinations of the foregoing) and Internet domain names any and all common law rights and registrations and applications for the registration thereof, and all extensions and renewals of any of the foregoing; (iii) copyrights and copyrightable works (including Software), registered copyrights and copyright applications, mask works, net lists and schematics; (iv) confidential and proprietary information including technology, know-how, trade secrets, unpatented inventions, ideas, algorithms and processes (including, without limitation, manufacturing and production processes and techniques, drawings, specifications, designs, plans, proposals, test data including pharmacological, biological, chemical, biochemical, toxicological and clinical test data, analytical and quality control data, stability data and customer and supplier lists and related information); (v) other intellectual property and proprietary information and (vi) all copies and tangible embodiments of the foregoing, such as instruction manuals, laboratory notebooks, prototypes, samples, specimens, studies and summaries.

(mm) "Investment Date" means January 23, 2008.

(nn) "Investment Documents" means the Master Agreement, the Call Option Agreement, the Investor Rights Agreement and the Stock Subscription Agreement.

(oo) "Investor Rights Agreement" means that certain Investor Rights Agreement, dated as of the Investment Date, by and among Isis, Ibis and AMI.

(pp) "Isis Licensed Intellectual Property" means the Intellectual Property set forth on Exhibit D.

(qq) [***]

(rr) "Knowledge" and terms of similar meaning (including, without limitation, "is aware of") mean (i) with respect to Ibis and Isis, the actual knowledge of any of the individuals set forth on Schedule 1(rr), after due investigation, including, without limitation, inquiry of Persons with subject matter knowledge, *provided* that (A) solely for purposes of Sections 5.1(l)(v), 5.1(l)(vi) and 5.1(l)(ix), "Knowledge" and terms of similar meaning (including, without limitation, "is aware of") mean the actual knowledge of any employee of Ibis or Isis, after due investigation, including, without limitation, inquiry of Persons with subject matter knowledge and (B) solely for purposes of Section 5.1(l), inquiry of Persons with subject matter knowledge shall include inquiry of the outside counsel involved in the development or prosecution of the Business IP or who conducted 'freedom to operate analyses' identified on Schedule 1(rr) and (ii) with respect to AMI, the actual knowledge of any of the individuals set forth on Schedule 1(rr), after due investigation.

(ss) "Licenses" means all licenses, permits, certificates of authority, variances, authorizations, approvals, registrations, franchises, orders and similar consents issued by any Governmental Authority or other Person, *provided*, that the term License shall not include any license or other right to use any Intellectual Property.

(tt) "Loss" means any loss, liability, demand, Claim, action, cause of action, cost, damage, diminution in value, deficiency, Tax, penalty, fine or expense (including interest, penalties, reasonable attorneys' fees and expenses and all amounts paid in investigation, defense or settlement of any of the foregoing and the enforcement of any related rights), whether or not arising out of third party claims.

(uu) "Management Presentations" means the Management Presentations of Ibis delivered to AMI pursuant to Section 2(h) of the Master Agreement.

(vv) "Master Agreement" means that certain Strategic Alliance Master Agreement, dated as of the Investment Date, by and among Isis, Ibis and AMI.

(ww) "Multiemployer Plan" has the meaning set forth in Section 3(37) of ERISA.

(xx) "Offering Memorandum" means the Offering Memorandum of Ibis, dated November 2006, as made available to AMI.

(yy) "[***]" means any payments, including, but not limited to royalty payments, license fees and milestone payments that are made by non-Affiliate third parties to [***] (or any of its Affiliates) in bona fide arms length transactions in consideration for one or more license or equivalent agreements that grant such non-Affiliate third party rights under any [***] (i) make, have made, use, sell, offer for sale or import any products by [***] to another party for a fee, in each case, where any of the foregoing conduct by such non-Affiliate third party in the absence of such rights under license or equivalent agreement would infringe (directly, contributorily, by inducement or otherwise), misappropriate or otherwise conflict with any [***].

(zz) "Permitted Encumbrances" means (i) liens for current property Taxes not yet due and payable, (ii) Encumbrances arising in connection with and solely as a result of Permitted Indebtedness and (iii) except with respect to Intellectual Property, other imperfections of title, restrictions or Encumbrances, if any, which imperfections, restrictions or Encumbrances do not, individually or in the aggregate, impair the continued use and operation of the assets used in the operation of the Business and do not affect the merchantability of the title to such assets to which they relate.

(aaa) "Permitted Indebtedness" means (i) accounts payable incurred in the ordinary course of business that are paid within forty-five (45) days of the date of invoice thereof, (ii) Indebtedness arising from existing and future lease obligations of Ibis under equipment leases that are capital leases in accordance with GAAP so long as the collateral for such capital leases is limited to the equipment acquired and the aggregate amount of such capital leases does not exceed [***] and (iii) Indebtedness incurred pursuant to the Corporate Services Agreement or the Contribution Agreement.

(bbb) "Person" means an individual, a partnership, a corporation, an association, a limited liability company, a joint stock company, a trust, a joint venture, an unincorporated organization, or a Governmental Authority (or any department, agency, or political subdivision thereof).

(ccc) "Pre-Closing Tax Period" means a Tax period ending on or before the Closing Date and the portion through the end of the Closing Date for any Tax period that includes (but does not end on) the Closing Date.

(ddd) "Post-Closing Tax Period" means a Tax period beginning after the Closing Date and, for any Tax period that includes (but does not end on) the Closing Date, the portion of such period beginning after the Closing Date.

(eee) "Products" means the T5000 Biosensor System (including kits) and any Successor Products.

(fff) "Purchase Offer" means any proposal or offer from any Person (other than AMI and its Affiliates in connection with the transactions contemplated hereby) or any agreement or offer relating to any (i) reorganization, liquidation, dissolution, share exchange, business combination or recapitalization of Ibis, (ii) merger or consolidation involving Ibis, (iii) purchase or sale of any assets or Capital Stock of Ibis (other than the purchase and sale of inventory and capital equipment in the ordinary course of business), (iv) distribution of Ibis'

existing or future products, (v) licensing of any Business IP from Ibis or (vi) any other transaction or business combination involving Ibis or its business or assets which would reasonably be expected to interfere with, impede or materially delay the transactions contemplated by the Transaction Documents or dilute the benefits thereof to AMI and its Affiliates.

(ggg) "Real Property" means the Leased Real Property.

(hhh) "Regulatory Authority" means any Governmental Authority that has responsibility for granting any licenses or approvals or granting pricing and/or reimbursement approvals necessary for the marketing and sale of medical devices or diagnostic products, including without limitation, the FDA, the European Medicines Agency and the United States Department of Health and Human Services.

(iii) "Release" means any spilling, leaking, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, depositing, disposing or other release into the environment (including the abandonment or discarding of barrels, drums, containers or other closed receptacles), including any dispersal, migration or other movement of any substance through or in air, soil, surface water, groundwater or property.

(jjj) "Representatives" means with respect to any Person, such Person's employees, directors, officers, Affiliates and authorized agents.

(kkk) "Schedule" means any of the Disclosure Schedules delivered to AMI herewith and incorporated herein pursuant to Section 10.11 hereof.

(lll) "SEC" or "Commission" means the United States Securities and Exchange Commission.

(mmm) "Securities Act" means the Securities Act of 1933, as amended.

(nnn) "Services" means using any Business IP to analyze samples containing nucleic acids and providing the results of such analyses to a third party for a fee.

(ooo) "Shares" means 114,251 shares of Common Stock issued to AMI pursuant to the Master Agreement, as may be held from time to time by AMI and its permitted assigns, representing approximately 10.25% of the issued and outstanding Common Stock.

(ppp) "Software" means any and all (i) computer programs, libraries, firmware and middleware, including any and all software implementations of algorithms, models and methodologies, whether in source code or object code, (ii) databases and compilations, including any and all data and collections of data, whether machine readable or otherwise, (iii) descriptions, flow-charts and other work product used to design, plan, organize and develop any of the foregoing and (iv) all programmer and user documentation, including user manuals and training materials, relating to any of the foregoing.

(qqq) "Stock Subscription Agreement" means the Stock Subscription Agreement dated as of June 27, 2008, by and among Ibis, Isis and AMI.

(rrr) "Subsidiary" means, with respect to a Person, any corporation, limited liability company, partnership, association or other business entity of which (i) if a corporation, a majority of the total voting power of shares of stock entitled (without regard to the occurrence of any contingency) to vote in the election of directors, managers or trustees thereof is at the time owned or controlled, directly or indirectly, by such Person or one or more of the other Subsidiaries of such Person or a combination thereof, or (ii) if a limited liability company, partnership, association or other business entity, a majority of the partnership or other similar ownership interest thereof is at the time owned or controlled, directly or indirectly, by such Person or one or more Subsidiaries of such Person or a combination thereof. For purposes hereof, a Person shall be deemed to have a majority ownership interest in a limited liability company, partnership, association or other business entity if such Person shall be allocated a majority of limited liability company, partnership, association or other business entity gains or losses or shall be or control any managing director or general partner of such limited liability company, partnership, association or other business entity.

(sss) "Successor Products" means any product that (i) relies upon [***] and determination of [***] by [***] using either the Ibis [***], each as in existence in the Business at the Closing, including as may be modified subsequently by AMI or (ii) is described in U.S. Patent No.'s [***].

(ttt) "T5000 Biosensor System" means the biosensor platform generally known as the T5000 Biosensor System, together with all equipment, hardware, Software, systems and other materials required for its use, or provided or recommended by Ibis, Isis or any of their respective Affiliates for its use, as well as all prior versions of the T5000 Biosensor System, including such systems known as "TIGER."

(uuu) "Tax" means any federal, state, local, or foreign income, gross receipts, license, payroll, employment, excise, severance, stamp, occupation, premium, windfall profits, environmental, customs and other duties, capital stock, franchise, profits, withholding, social security, unemployment, disability, real property, personal property, sales, use, transfer, registration, value added, alternative or add-on minimum, estimated, or other tax of any kind whatsoever, including any interest, penalty, or addition thereto, whether disputed or not, and including any obligation to indemnify or otherwise assume or succeed to the Tax liability of any other Person.

(vvv) "Tax Return" means any return, declaration, report, claim for refund, or information return or statement relating to Taxes, including any schedule or attachment thereto, and including any amendment thereof.

(www) "Third Party Payments" means payments, including, but not limited to damage awards, royalty payments, license fees and milestone payments, that are made by [***] to a third party, which are based upon making, having made, using, selling, offering for sale or importing [***], under order of a Governmental Authority or license agreements or equivalent agreements with the third party to obtain rights under any United States or foreign copyrights, patent applications or patents that are [***] to make, have made, use, sell, offer for sale or import any [***].

(xxx) "Transaction Documents" means the Master Agreement, the Investor Rights Agreement, the Stock Subscription Agreement, the Call Option Agreement, the Transition Services Agreement and this Agreement.

(yyy) "Transfer" means, with respect to Capital Stock, any sale, pledge, hypothecation, assignment, Encumbrance or other transfer or disposition, whether directly, indirectly, voluntarily, involuntarily, by operation of Law, pursuant to judicial process or otherwise and, when the context so requires, the act of doing any of the foregoing.

Section references for definitions of defined terms defined in the body of this Agreement rather than in this Section 1.

Defined Term	Section
"§ 338(h)(10) Election"	8.6(g)
"Abbott"	Preamble
"ADR"	10.8
"Agreement"	Preamble
"AMI"	Preamble
"AMI Group"	8.2(a)
"AMI Proceeding"	8.6(e)(ii)
"Applicable AMI Proceeding"	8.6(e)(ii)
[***]	
"Business IP"	5.1(l)(i)
"Closing"	3.1
"Closing Date"	3.1
"Closing Purchase Price"	2.2
"Disclosing Party"	8.8(a)
"Disclosure Schedules"	Section 5
"Earnout Payments"	2.3(e)
"Earnout Period"	2.3(a)
"Earnout Rate"	2.3(a)
"ERISA Affiliate"	5.1(p)(ii)
"ERISA Plans"	5.1(p)(ii)
"FDA"	5.1(q)(i)
"Financial Statements"	5.1(t)(i)
"Government Contracts"	5.1(l)(ii)

"HSR Act"	4.1(d)
"Ibis"	Preamble
"Ibis Contracts"	5.1(x)(i)
"Ibis Employees"	8.11(a)
"Indemnified Party"	8.2(e)
"Indemnifying Party"	8.2(e)
"Insurance Policies"	5.1(y)
"IP Contracts"	5.1(l)(ii)
"Isis"	Preamble
"Isis Proceeding"	8.6(e)(i)
"Isis Retirement Plans"	8.11(d)
"Leased Real Property"	5.1(w)(ii)
"Leasehold Improvements"	5.1(w)(ii)
"Leases"	5.1(w)(ii)
"Material Adverse Effect"	4.1(j)

“Material Licenses”	5.1(q)(ii)
“Most Recent Balance Sheet”	5.1(t)(i)
“Noncompete Period”	8.9(a)
“Nonsolicitation Period”	8.9(c)
“Note”	7.12
“Parties”	Preamble
“Party”	Preamble
“Plans”	5.1(p)(ii)
“Pre-Existing Business”	8.9(b)
[***]	
“Purchase Price”	2.2
“Rate Reserve Limit”	8.15
[***]	
“Receiving Party”	8.8(a)
“Remaining Shares”	Recitals
“Restricted Assets”	2.5
“Seller Group”	8.2(b)
“Special AMI Claims”	8.2(e)(iii)

“Straddle Period”	8.6(c)(ii)
“Third Party Claim”	8.2(e)
“Transaction Value”	2.2
“Transition Services Agreement”	4.1(k)
“WARN Act”	8.11(b)

Section 2. BASIC TRANSACTION; PURCHASE PRICE.

2.1 Sale and Transfer of the Remaining Shares. Subject to the terms and conditions of this Agreement, at the Closing, Isis shall sell, convey, assign, transfer and deliver to AMI all of the Remaining Shares, free and clear of all Encumbrances, and AMI shall purchase, acquire and accept the Remaining Shares from Isis.

2.2 Purchase Price. The purchase price (the “Purchase Price”) for the Remaining Shares shall be equal to (i) $175,000,000 (the “Transaction Value”), minus (ii) the amount of any Indebtedness of Ibis as of the Closing (not including the amount of any Indebtedness that is Permitted Indebtedness under clauses (i) or (ii) of the Permitted Indebtedness definition), plus (iii) the Earnout Payments. The “Closing Purchase Price” is an amount equal to (x) the Transaction Value, minus (y) the amount of any Indebtedness of Ibis as of the Closing (not including the amount of any Indebtedness that is Permitted Indebtedness under clauses (i) or (ii) of the Permitted Indebtedness definition).

2.3 Earnout Payments.

(a) Subject to Sections 2.3(e) and 2.3(g), from and after the Closing Date until December 31, 2025 (the “Earnout Period”), Ibis will pay to Isis an amount equal to five percent (5%) (the “Earnout Rate”) of cumulative Ibis Net Sales that are (i) in excess of the Earnout Threshold and (ii) less than or equal to $2,100,000,000. Such amounts payable to Isis will be reduced by an amount equal to [***] of any [***], but in no event will such amounts for such Ibis Net Sales be less than two and a half percent (2.5%) of such cumulative Ibis Net Sales.

(b) For cumulative Ibis Net Sales during the Earnout Period that are in excess of $2,100,000,000, the Earnout Rate will reduce from 5% to 3%. The corresponding amounts payable to Isis will be reduced by an amount equal to [***] of any [***], but in no event will such amounts for such Ibis Net Sales be less than one and a half percent (1.5%) of such cumulative Ibis Net Sales.

(c) In calculating the amount of any reduction to the earn-out payments permitted by the second sentence of either Section 2.3(a) or Section 2.3(b) that result from any [***] that are [***], the amount of such [***] [***] will be [***] of the Earnout Period from the date of such [***]. For example, if Ibis makes a [***] in the form of [***] equal to [***] to [***] which, in AMI’s reasonable judgment was [***] and such [***] was made in 2015, then, in each calendar quarter, Ibis would be able to reduce the corresponding amounts

payable for such quarter by [***], in each case subject to the applicable 2.5% or 1.5% floor under Section 2.3(a) or Section 2.3(b).

(d) The earnout amounts described in Sections 2.3(a) and 2.3(b) will be payable on a quarterly basis, within [***] days after the last day of each calendar quarter, by wire transfer of immediately available funds to an account designated by Isis. Within [***] [***] days of the end of each calendar quarter, Ibis will deliver to Isis its non-binding, preliminary, good faith estimate of Ibis Net Sales for such calendar quarter. All amounts included in Ibis Net Sales shall be in United States funds collectible at par in Chicago, Illinois. With respect to Product or Service revenues, [***], or [***] that are used in the calculation of Ibis Net Sales and are in monies other than United States dollars, the amount to be used will first be determined in the foreign currency of the country for such monies and then converted into equivalent United States funds using the same conversion methodology that Abbott uses to prepare its financial statements filed with the SEC.

(e) Notwithstanding the foregoing, Sections 2.3(a) through 2.3(c), (i) the earnout amounts described in Sections 2.3(a) and 2.3(b) will be payable only on cumulative Ibis Net Sales in excess of the Earnout Threshold, (ii) no such earnout amounts will be payable in any calendar year in which total Ibis Net Sales in such calendar year were less than or equal to [***], (iii) in any calendar year in which Ibis Net Sales exceed [***] and cumulative Ibis Net Sales exceed the Earnout Threshold, the earnout amounts described in Sections 2.3(a) and 2.3(b) will be payable with respect to all Ibis Net Sales in such calendar year which are in excess of the Earnout Threshold and (iv) all Ibis Net Sales, regardless of whether earnout amounts are payable

thereon, will be included in cumulative Ibis Net Sales for purposes of determining the applicable Earnout Rate. For example, if Ibis Net Sales in each of the calendar years 1 and 3 are equal to [***] and Ibis Net Sales in each of the calendar years 2 and 4 are equal to [***], no earnout amounts would be payable in calendar years 1 through 3, but earnout amounts would be payable with respect to the entire [***] in Ibis Net Sales in calendar year 4. The earnout amounts payable by Ibis to Isis pursuant to this Section 2.3 are referred to herein as the "Earnout Payments."

(f) Ibis shall maintain its books and records used to determine Ibis Net Sales, [***], and [***] for a period of three (3) years from the date of the Earnout Payment to which they pertain. Ibis shall make such books and records available for inspection by third party representatives of Isis approved in writing (which approval shall not be unreasonably withheld, conditioned or delayed) once per calendar year at reasonable times and upon reasonable written advance notice from Isis. All information contained in these books and records shall be Confidential Information and will be used only for the purpose of determining the accuracy of Ibis' calculation of any Earnout Payment.

(g) Notwithstanding any provision of this Agreement or any other Transaction Document to the contrary, except with respect to any [***] arising as a result of or in connection with a breach of the representations and warranties set forth in Section 5.1(l)(v), the Earnout Payment reductions set forth in Sections 2.3(a) and 2.3(b) will be the AMI Group's sole and exclusive remedy for any [***].

2.4 [Reserved]

2.5 Restricted Assets. Notwithstanding any other provision in this Agreement to the contrary, this Agreement shall not constitute an agreement to assign or transfer any interest in any Contract, asset, claim, right or benefit the assignment or transfer of which is otherwise contemplated by the transactions contemplated by this Agreement to the extent such assignment or transfer (or attempt to make such an assignment or transfer) without the consent or approval of a third party would constitute a breach or other contravention of the rights of such third party, or affect adversely the rights of any Party or their Affiliates thereunder (such assets being collectively referred to herein as "Restricted Assets"). Any assignment or transfer of a Restricted Asset shall be made subject to such consent or approval being obtained. If any such consent or approval is not obtained prior to the Closing, (a) the assigning or transferring Party shall continue to use its commercially reasonable efforts to cooperate with the other Party in attempting to obtain any such consent or approval and (b) establish alternative arrangements (such as a license, sublease, subcontract or operating agreement) until such time as such consent or approval has been obtained which results in the assignee or transferee Party receiving all the benefits and bearing all the burdens with respect to any such Restricted Asset (subject to Section 8.4, pursuant to which Isis shall be liable for and pay all out-of-pocket costs and expenses associated with obtaining third party consents associated with any Ibis Contract or Restricted Asset in excess of [***] in the aggregate).

Section 3. CLOSING OF THE TRANSACTION.

3.1 The Closing. Subject to the satisfaction or waiver of the conditions set forth herein, the closing of the transactions contemplated by this Agreement (the "Closing") shall take place at the offices of Kirkland & Ellis LLP in Chicago, Illinois, at 10:00 a.m. Central Time on the third Business Day following the satisfaction or waiver of all conditions to the obligations of the Parties to consummate the transactions contemplated, or on such other date, time and place as the Parties may mutually agree in writing (the "Closing Date"), and the Closing shall be deemed effective as of 12:01 a.m. Pacific Time on the Closing Date.

3.2 Deliveries at the Closing. At the Closing:

(a) Isis shall deliver to AMI (i) the various certificates, agreements, instruments and documents referred to in Section 4.1 below and (ii) such other instruments of sale, transfer, conveyance and assignment as AMI reasonably may request;

(b) AMI shall deliver to Isis (i) the Closing Purchase Price, via wire transfer of immediately available funds to an account designated in writing by Isis at least five (5) Business Days prior to the Closing Date, and (ii) the various certificates, agreements, instruments and documents referred to in Section 4.2 below;

(c) Isis shall deliver to Ibis all books, records and other materials of Ibis or related to or used by Ibis in the Business, including the corporate minute book and stock ledger for Ibis (unless otherwise specifically set forth in the Transition Services Agreement); and

(d) Isis shall deliver to AMI one or more compact discs or other electronic media containing the contents of the electronic dataroom maintained by Isis at [***] as of the date that is three Business Days prior to the date hereof, together with a certificate of an

authorized officer certifying that such compact discs contain true, accurate and complete copies of the materials in such dataroom as of such date.

Section 4. CONDITIONS TO OBLIGATION TO CLOSE.

4.1 Conditions to Obligation of AMI. The obligation of AMI to consummate the transactions to be performed by it in connection with the Closing is subject to satisfaction of the following conditions:

(a) Each of the representations and warranties of Isis set forth in this Agreement shall be true and correct in all material respects at and as of the date hereof and as of the Closing Date (disregarding any materiality or Material Adverse Effect qualifications contained therein, other than such qualifications contained in Section 5.1(aa)); *provided*, that any representation or warranty of Isis set forth in this Agreement that is made as of any date other than the date hereof shall be true and correct as of such date in all material respects (disregarding any materiality or Material Adverse Effect qualifications contained therein).

(b) Each of Isis and Ibis shall have performed and complied in all material respects with each of their covenants hereunder through the Closing.

(c) No Claim shall be pending before any court, arbitrator, other body or administrative agency of any Governmental Authority wherein an unfavorable injunction, judgment, order, decree, ruling or charge would prevent consummation of any of the transactions contemplated by this Agreement (and no such injunction, judgment, order, decree, ruling or charge shall be in effect).

(d) All filings with and authorizations and approvals of Governmental Authorities that are required for the consummation of the transactions contemplated hereby shall have been duly made and obtained on terms reasonably satisfactory to AMI. Without limiting the generality of the foregoing, all applicable waiting periods (and any extensions thereof) under the Hart Scott Rodino Antitrust Improvements Act of 1976, as amended (the "HSR Act"), shall have expired or otherwise been terminated.

(e) Isis shall have delivered to AMI (i) a certificate from an officer of Isis to the effect that each of the conditions specified in Section 4.1(a), Section 4.1(b) and, except for the matters expressly set forth on the Disclosure Schedules, Section 4.1(j), is satisfied in all respects, (ii) a copy of the resolutions of the governing body of each of Isis and Ibis approving the transactions contemplated by this Agreement, certified by an officer of each of Isis and Ibis, respectively, (iii) certificates from appropriate authorities, dated as of or about the Closing Date, as to the good standing and qualification to do business of Ibis in its jurisdiction of incorporation, (iv) such other documents or instruments as are required to be delivered at the Closing pursuant to the terms hereof and (v) such other documents or instruments as AMI reasonably requests to effect the transactions contemplated hereby. Nothing in this Section 4.1(e) or the certificate delivered pursuant hereto will limit or otherwise affect AMI's rights under Section 4.1(j).

(f) Isis shall tender to AMI a certificate representing the Remaining Shares duly and validly endorsed for transfer in favor of AMI or accompanied by a separate

stock power duly and validly executed by Isis and otherwise sufficient to vest in AMI legal and beneficial ownership of the Remaining Shares.

(g) Isis and AMI shall have received all other authorizations, consents, and approvals of Governmental Authorities referred to in Sections 5.1(c) and 5.1(d).

(h) Ibis shall have the benefit of all Licenses necessary to conduct the Business as it had been conducted prior to the Closing and as contemplated to be conducted immediately thereafter.

(i) Isis shall have obtained (A) payoff letters for any Indebtedness of Ibis to be paid by AMI on behalf of Isis at the Closing and (B) releases of any and all Encumbrances on the Remaining Shares or the assets of Ibis (except, with respect to the assets of Ibis, Permitted Encumbrances), all on terms reasonably satisfactory to AMI.

(j) Since the Investment Date, there shall have been no occurrence or disclosure of any event, circumstance or state of facts which has, or would reasonably be expected to have, a material adverse effect on the business, assets, condition (financial or otherwise), operations, operating results, employee relations, customer relations or supplier relations of Ibis (a "Material Adverse Effect"). Notwithstanding the foregoing or any other provision in this Agreement to the contrary, the disclosures set forth in the Disclosure Schedules shall not be considered in determining whether the condition specified in this Section 4.1(j) has been met.

(k) Isis and Ibis shall have executed and delivered to AMI the Transition Services Agreement substantially in the form attached hereto as Exhibit E, the terms of which shall provide that (i) subject to Section 8.14, in no event will AMI and Ibis together be required to pay to Isis more than $[***] in the aggregate for the Initial Services (as defined in the Transition Services Agreement) provided by Isis thereunder, (ii) Isis will provide only the categories of services set forth on Exhibit E-1 attached hereto, and (iii) Ibis will not occupy Isis' facilities nor will Isis be required to provide services to Ibis after [***] (the "Transition Services Agreement"), and the Transition Services Agreement shall be in full force and effect.

(l) Isis shall have executed and delivered to AMI a non-foreign affidavit dated as of the Closing Date and in form and substance required under the Treasury Regulations issued pursuant to Code § 1445 stating that Isis is not a "Foreign Person" as defined in Code § 1445.

(m) There shall not have been any material breach of any of the terms and provisions of the Transaction Documents that has not been waived by AMI.

(n) Except as contemplated by Section 2.5 and the Transition Services Agreement, Ibis shall be entitled to fully exercise without restriction or limitation all legal and beneficial rights under the Ibis Contracts (including the Government Contracts) and all other assets, properties and rights related to, used in or necessary to operate and conduct the Business in all respects in the manner conducted on and prior to the Closing Date and as contemplated to be conducted from and after the Closing Date.

[***]AMI may waive any condition specified in this Section 4.1 if it executes a writing so stating at or prior to the Closing. In the event of any such waiver, AMI shall be deemed to have waived any claim against Isis for failure to satisfy such condition; *provided* that, except to the extent specifically and expressly set forth in such waiver, any such waiver shall not limit AMI's right to recovery hereunder for a breach by either Isis or Ibis of any other provision of this Agreement.

4.2 Conditions to Obligation of Isis. The obligation of Isis to consummate the transactions to be performed by it in connection with the Closing is subject to satisfaction of the following conditions:

(a) Each of the representations and warranties of AMI set forth in this Agreement shall be true and correct in all material respects at and as of the date hereof and as of the Closing Date.

(b) AMI shall have performed and complied in all material respects with each of its covenants hereunder through the Closing;

(c) No Claim shall be pending before any court, arbitrator, other body or administrative agency of any Governmental Authority wherein an unfavorable injunction, judgment, order, decree, ruling or charge would prevent consummation of any of the transactions contemplated by this Agreement (and no such injunction, judgment, order, decree, ruling or charge shall be in effect).

(d) All filings with and authorizations and approvals of Governmental Authorities that are required for the consummation of the transactions contemplated hereby shall have been duly made and obtained on terms reasonably satisfactory to Isis. Without limiting the generality of the foregoing, all applicable waiting periods (and any extensions thereof) under the HSR Act shall have expired or otherwise been terminated.

(e) AMI shall have delivered to Isis a certificate of AMI to the effect that each of the conditions specified above in Section 4.2(a) and Section 4.2(b) is satisfied in all respects.

(f) AMI (and any other Abbott Holders (as defined in the Investor Rights Agreement)) shall have executed and delivered to Isis a written consent in form reasonably satisfactory to AMI and Isis, consenting to the transactions contemplated by Section 7.10.

Isis may waive any condition specified in this Section 4.2 if it executes a writing so stating at or prior to the Closing. In the event of any such waiver, Isis shall be deemed to have waived any claim against AMI for failure to satisfy such condition; *provided* that, except to the extent specifically and expressly set forth in such waiver, any such waiver shall not limit Isis' right to recovery hereunder for a breach by AMI of any other provision of this Agreement.

Section 5. REPRESENTATIONS AND WARRANTIES.

5.1 Representations and Warranties of Isis. As a material inducement to AMI to enter into this Agreement, except as set forth in the corresponding Section of the Disclosure Schedules delivered to AMI herewith on the date hereof (the "Disclosure Schedules"), Isis hereby represents and warrants the following representations and warranties are as of the date hereof, and will be as of the Closing Date, true and correct:

(a) Power and Authority. Each of Ibis and Isis (i) has the power, authority and the legal right to enter into each of the Transaction Documents and to perform its obligations hereunder and thereunder, and (ii) has taken all necessary action required to authorize the execution and delivery of each of the Transaction Documents and the performance of its obligations hereunder and thereunder.

(b) Enforceability. Each of the Transaction Documents has been duly executed and delivered on behalf of Ibis and Isis and constitutes a legal, valid and binding obligation of each such Party and is enforceable against each such Party in accordance with its terms subject to the effects of bankruptcy, insolvency or other Laws of general application affecting the enforcement of creditor rights.

(c) Governmental Authority; Consents. All necessary consents, approvals and authorizations of all Governmental Authorities and other parties required to be obtained by Ibis and Isis in connection with the execution and delivery of each of the Transaction Documents and the performance of their obligations hereunder and thereunder have been obtained.

(d) No Conflicts. The execution and delivery of each of the Transaction Documents by each of Ibis and Isis and the performance of each such Party's obligations hereunder and thereunder, with or without the passage of time or giving of notice, (i) do not and will not conflict with or violate any requirement of Applicable Law or any provision of the certificate of incorporation, bylaws or any similar instrument of such Party, as applicable (ii) do not and will not require any notice, conflict with, violate, or breach or constitute a default or require any consent or give rise to any termination or acceleration right or the creation of any Encumbrance on the Shares, the Additional Shares or the Remaining Shares or any of the properties or assets of Ibis under, any contractual obligation by which such Party is bound or subject to and (iii) do not and will not cause the suspension, revocation, impairment, forfeiture or nonrenewal of any License applicable to Ibis, the Business or any of Ibis' operations, assets or properties.

(e) Due Organization; Qualification. Each of Ibis and Isis is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to enter into each of the Transaction Documents. Except as would not reasonably be expected to have a Material Adverse Effect, Ibis has obtained and currently maintains all qualifications to do business as a foreign corporation in all jurisdictions in which the character of the Business requires it to be so qualified. Ibis has all requisite power and authority and all authorizations and Licenses necessary to own, operate or conduct the Business.

(f) Subsidiaries. Ibis does not own or control any Capital Stock or other interest of any Person. Ibis is not a participant in any joint venture, partnership, limited liability company or similar arrangement. Since its inception Ibis has not merged with, acquired all or substantially all of the assets of (except pursuant to the Contribution Agreement) or acquired the Capital Stock of or any interest in any Person. Ibis does not hold the right to acquire any Capital Stock or interest in any other Person or have any obligation to make any investment in any Person and no such rights, Capital Stock or interests are necessary for the operation of the Business. Isis does not control or possess the power, directly or indirectly to control the management, actions or policies of Regulus Therapeutics, LLC.

(g) Capitalization; Voting Rights.

(i) The authorized Capital Stock of Ibis consists of 1,228,501 shares of Common Stock, par value $0.001 per share, 1,228,501 shares of which are issued and outstanding, 1,000,000 of which are held by Isis and 228,501 shares of which are held by AMI.

(ii) The issued and outstanding Capital Stock of Ibis as of the Closing will consist exclusively of the Shares, the Additional Shares and the Remaining Shares. Except as set forth in the Investor Rights Agreement, Ibis does not have any obligations to issue or redeem any shares of Capital Stock and Ibis has not issued any Capital Stock other than the Shares, the Additional Shares and the Remaining Shares. No Capital Stock issued by Ibis is listed on any stock exchange or unregulated market. Other than the Transaction Documents, there are no agreements with Isis or Ibis or any other Person with respect to the voting or Transfer of the Remaining Shares.

(iii) The Remaining Shares are: (A) duly authorized, validly issued, fully paid and nonassessable; (B) issued in compliance with all applicable state and federal Laws concerning the issuance of Capital Stock; and (C) free and clear of all Encumbrances other than the Call Option; *provided,* that the Remaining Shares may be subject to restrictions on Transfer under state and/or federal securities Laws as set forth herein or as otherwise required by such Laws at the time a Transfer is proposed.

(iv) The sale of the Remaining Shares to AMI hereunder is not subject to any preemptive rights, rights of first refusal or similar rights.

(h) Agreements; Liabilities.

(i) There are no judgments, orders, writs or decrees to which Ibis or Isis is a party currently pending or, to Isis' or Ibis' Knowledge, threatened which would prevent Ibis or Isis from entering into the Transaction Documents or issuing or Transferring the Remaining Shares pursuant to the terms of the Transaction Documents.

(ii) Ibis has not (A) accrued, declared or paid any dividends, or authorized or made any distribution upon or with respect to any class or series of its Capital Stock, (B) incurred or guaranteed any Indebtedness (other than Permitted Indebtedness), (C) made any loans or advances to any Person, other than advances for reasonable travel expenses to Ibis employees in the ordinary course of business, or

(D) sold, exchanged, licensed or otherwise disposed of any of its tangible assets, other than the sale of its inventory in the ordinary course of business.

(iii) Ibis has no material obligations or liabilities (whether accrued, absolute, or to Isis' or Ibis' Knowledge contingent, unliquidated or otherwise, whether due or to become due and regardless of when or by whom asserted), including, without limitation, Taxes, except (A) obligations under the Ibis Contracts made available to AMI or under Contracts entered into in the ordinary course of business which, because of the dollar thresholds set forth in Sections 5.1(l) and 5.1(x), are not required pursuant to Sections 5.1(l) and 5.1(x) below to be described on Schedules 5.1(l) or 5.1(x) (but not liabilities for breaches of any such Contracts), (B) liabilities reflected on the Most Recent Balance Sheet, (C) liabilities and obligations which have arisen after the date of the Most Recent Balance Sheet in the ordinary course of business (none of which is material or is a liability for breach of contract, tort, infringement (directly, contributorily, by inducement or otherwise), Claim or warranty (other than warranty claims arising in the ordinary course of business in connection with the sale of Products or under Ibis Contracts made available to AMI, none of which warranty claims individually or in the aggregate would reasonably be expected to have a Material Adverse Effect) and (D) other liabilities and obligations to the extent expressly disclosed in Schedule 5.1(h)(iii).

(i) Obligations to Related Parties. There are no obligations of Ibis to Affiliates, officers, directors or employees of Ibis or Isis other than (i) for payment of salary to employees of Ibis for services rendered in the ordinary course of business, (ii) reimbursement to employees of Ibis for reasonable expenses incurred in the ordinary course of business on behalf of Ibis, (iii) standard employee benefits made generally available to all employees, pursuant to the Plans described on Schedule 5.1(p)(ii), (iv) the Bonus Arrangement or (v) Ibis' rights and obligations to Isis under the Contribution Agreement and Corporate Services Agreement. To Isis' and Ibis' Knowledge, all of the Contracts to which Ibis is a party or by which the Business or any of its assets is bound have been negotiated on an arms length basis.

(j) Title to Properties and Tangible Assets; Liens, Etc. Ibis has good and marketable title to its properties and tangible assets and good and valid title to its leasehold estates, in each case subject to no Encumbrance other than (i) Permitted Encumbrances and (ii) rights of the U.S. federal government in certain equipment purchased using government funds, as set forth on Schedule 5.1(j). The tangible assets of Ibis have been maintained in accordance with normal industry practice and are in good operating condition and repair (except for ordinary wear and tear).

(k) Sufficiency of Assets.

(i) Except for the services, funding and facilities provided under the Corporate Services Agreement, Ibis has all assets, properties and rights used in or necessary to operate or conduct the Business in all respects.

(ii) Except the services, funding and facilities provided under the Corporate Services Agreement and indirectly, via the Remaining Shares, Isis and its Affiliates do not have any right, title or

interest in or to any asset, property, title or interest that is used in or necessary to operate or conduct the Business as conducted on and prior to the Closing Date or as contemplated to be conducted by Ibis and Isis after the Closing Date as reflected in the Offering Memorandum and Management Presentations. Pursuant to the Contribution Agreement, Isis has transferred to Ibis all assets, properties and rights Isis owned or which are or were used in or necessary to operate or conduct the Business except the services, funding and facilities provided under the Corporate Services Agreement. No person employed by the Division prior to the date of the Contribution Agreement is currently employed by Isis and no former employee of Ibis or the Division is or has been employed by Isis.

(l) Intellectual Property.

(i) Schedule 5.1(l)(i) sets forth a complete and correct list of all of the following Intellectual Property used in or necessary to operate or conduct the Business (whether owned by Ibis or any other Person), and indicates with respect to each item, whether Ibis owns or licenses such Intellectual Property and the owner of any Intellectual Property covered by such license: (A) patented or registered Intellectual Property and pending patent applications or other applications for registrations of Intellectual Property (including jurisdiction, registration and application number, as applicable, and record owner), (B) registered and material unregistered trademarks, service marks, trade names, and Internet domain names, (C) Software (other than unmodified, commercially available, off-the-shelf Software purchased or licensed for less than an individual cost of [***] and a total cost of [***] in the aggregate for all such licenses), (D) material algorithms embodied in the Products

and any other material trade secrets; and (E) all other material Intellectual Property used in or necessary to operate or conduct the Business (including, without limitation, all Intellectual Property set forth or required to be set forth in the following Schedules to the Contribution Agreement: Schedule 2.1 (Ibis Business Assets), Schedule 2.2 (Ibis Business Patents), Schedule 2.5 (Ibis Trademarks) and Schedule 2.6 (Ibis Business Software)) (all Intellectual Property described in the foregoing, (A) through (E), collectively, (without regard to whether such Intellectual Property is set forth on Schedule 5.1(l)(i)) "Business IP").

(ii) Schedule 5.1(l)(ii) sets forth a complete and correct list of all of the following Contracts (other than licenses for unmodified, commercially available, off-the-shelf Software purchased or licensed for less than an individual cost of [***] and a total cost of [***] in the aggregate for all such licenses) relating to the Business IP (collectively, the "IP Contracts"): (A) Contracts in which Ibis or Isis or any of their respective Affiliates is a licensee or sublicensee of Business IP; (B) Contracts in which Ibis or Isis or any of their respective Affiliates is a licensor or sublicensor of Business IP; (C) Contracts to which Ibis or Isis or any of their respective Affiliates is a party, or by which any of the Business IP is bound, that give any third party any right, title or interest in or to any such Business IP; (D) Contracts with any Governmental Authority wherein any portion of the Business IP was developed or used ("Government Contracts"); and (E) Contracts that restrict Ibis' rights in or use or disclosure of Business IP.

(iii) Ibis owns and possesses all right, title and interest in and to, free and clear of all Encumbrances (other than the rights of Governmental Authorities under Government Contracts identified in Schedule 5.1(l)(iii) to the Intellectual Property identified in such Schedule) or has a valid and enforceable license to use (pursuant to a written license agreement set forth and described in Schedule 5.1(l)(ii) or a written license for unmodified, commercially available, off-the-shelf Software purchased or licensed for less than an individual cost of [***] and a total cost of [***] in the aggregate) the Business IP.

(iv) Neither Isis nor any of its Affiliates (other than Ibis) has any right, title or interest in or to any of the Business IP.

(v) To Isis' or Ibis' Knowledge, neither Ibis, nor with respect to the Business, Isis, has infringed (directly, contributorily, by inducement or otherwise), misappropriated or otherwise conflicted with, and the operation of the Business (including the development, manufacture and commercialization of the T5000 Biosensor System, the [***], and the assay kits specifically listed in the [***]) does not and will not infringe (directly, contributorily, by inducement or otherwise), misappropriate or otherwise conflict with, the patents, trademarks, copyrights or trade secrets of any Person, and neither Ibis nor Isis is aware of any facts that indicate a likelihood of any of the foregoing (including without limitation, oral or written demands or offers to license any Intellectual Property from any Person). With respect to whether the operation or conduct of the Business has or will infringe (directly, contributorily, by inducement or otherwise), misappropriate or otherwise conflict with patent, trademark, copyright or trade secrets of any Person (other than Ibis or Isis or their respective Affiliates), the Parties hereto are relying upon the representations and warranties contained in this Section 5.1(l)(v) and not the representations and warranties contained in Sections 5.1(k)(i), 5.1(l)(viii) or 5.1(l)(ix).

(vi) All of the Business IP is valid and to Isis' or Ibis' Knowledge enforceable. Isis and Ibis have taken all necessary actions to maintain and protect all of the Business IP, including, without limitation, entering into confidentiality agreements with each of its employees, consultants and independent contractors, and customers and vendors as necessary so as not to adversely affect the validity or enforceability thereof and have complied with disclosure requirements as provided by any Government Contract. Neither Ibis nor Isis has disclosed any source code for any Software included in the Business IP to any Person in a manner that would impair the trade secret or other Intellectual Property protection of such source code. There are no claims, oppositions or cancellation proceedings that either were made or brought within the past [***] years, or are presently pending or, to Isis' or Ibis' Knowledge, threatened, against either Ibis or Isis contesting the validity, use, ownership, enforceability or registrability of any Business IP. Neither Ibis nor Isis is aware of any basis for any such claim, opposition or cancellation proceeding, and neither Ibis nor Isis has received any notices regarding any of the foregoing. No loss or expiration of any material Business IP is pending or reasonably foreseeable or, to Isis' or Ibis' Knowledge, threatened, except for patents expiring at the end of their statutory terms (and not as a result of any act or omission by either Ibis or Isis, including, without limitation, a failure to pay any required maintenance fees) or limitations to the scope of claims of any pending patent application

made during the ordinary course of prosecuting such pending patent applications. Complete copies of all file histories for issued patents and pending patent applications of the Business IP owned or held by either Ibis or Isis have been provided to AMI.

(vii) To Isis' or Ibis' Knowledge, (A) no Person has infringed (directly, contributorily, by inducement or otherwise) or misappropriated any of the Business IP and (B) no Person is infringing (directly, contributorily, by inducement or otherwise) or misappropriating any of the Business IP.

(viii) Ibis has sufficient right, title and interest in and to the Business IP: (A) to conduct the Business, including the development, manufacture and commercialization of the T5000 Biosensor System (including the [***] and the assay kits specifically listed in the [***] on a worldwide basis, with no payment obligation to any Person, except pursuant to an IP Contract, and (B) to make, have made, import, use, offer for sale, or sell any product (including [***] currently marketed by the Business and the assay kits specifically listed in the [***] without infringing (directly, contributorily, by inducement or otherwise), misappropriating or conflicting with any Intellectual Property rights of any Person. The Business IP is and will be as of the Closing Date, owned by or available for use by Ibis on terms and conditions identical to those under which it was owned or used by Ibis and the Business prior to the date hereof.

(ix) To Isis' or Ibis' Knowledge, Ibis has sufficient right, title and interest in and to the Business IP: (A) to develop, manufacture and commercialize the [***] on a worldwide basis, with no payment obligation to any Person, except pursuant to an IP Contract made available to AMI, and (B) to make, have made, import, use, offer for sale, or sell the [***] without infringing (directly, contributorily, by inducement or otherwise), misappropriating or conflicting with any Intellectual Property rights of any Person.

(x) No funding, facilities or resources of a Governmental Authority, university, college, other educational institution or research center or funding from third parties was used in the development of any of the Business IP and no Governmental Authority, university, college, other educational institution or research center has any claim or right in or to any of the Business IP.

(xi) Each current or former employee of each Isis Party or any of their respective Affiliates, who was involved in, or who contributed to, the creation or development of any Business IP, executed the standard form of proprietary rights agreement set forth in Schedule 5.1(l)(xi) upon commencement of his or her employment and each such current or former employee and any consultant or independent contractor who was involved in, or who contributed to, the creation or development of any Business IP has validly assigned all right, title and interest in and to such Business IP to Ibis.

(xii) None of the Transaction Documents nor the transactions contemplated by any of the Transaction Documents would result in or reasonably be expected to result in: (A) Ibis, AMI or any of their respective Affiliates granting to any Person any right to or with respect to any Intellectual Property owned by, or licensed to,

any of them as a result of any Encumbrance or Contract to which, Ibis or any of their Affiliates is a party or bound by, (B) other than standard non-solicitation agreements entered into in the ordinary course of business and made available to AMI, Ibis, AMI or any of their respective Affiliates being bound by, or subject to, any non-compete or other material restriction on the operation or scope of their respective businesses as a result of any Encumbrance or Contract to which Isis, Ibis or any of their Affiliates is a party or bound by, (C) other than as contemplated by the Acquisition Agreement, Ibis, AMI or any of their respective Affiliates being obligated to pay any royalties or other material amounts, to increase or accelerate any royalty or payment obligation, or to offer any discounts, to any Person as a result of any Encumbrance or Contract to which Isis, Ibis or any of their Affiliates is a party or bound by, or (D) any adverse effect on Ibis' right, title or interest in and to any of the Business IP.

(xiii) All components of the current version of the T5000 Biosensor System perform in all material respects in accordance with their currently advertised, displayed, distributed or published specifications. All services that have been performed in the conduct of the Business were performed in material conformity with the terms and requirements of the related Contracts and all Applicable Laws. All Software included in the Business IP is free of any disabling codes or instructions, timer, copy protection device, clock, counter or other limiting design or routing and any "back door," "time bomb," "Trojan horse," "worm," "drop dead device," "virus" or other similar disabling codes, Software routines or hardware components. No open source, public source or other Software that is licensed pursuant to a license that purports to require the distribution of, or access to, source code or purports to restrict one's ability to charge for distribution of Software (including, without limitation, any version of any Software licensed pursuant to any GNU general public license or limited general public license or other Software), was used in, incorporated into, integrated or bundled with any Software that has been used in the T5000 Biosensor System or any other product that has been distributed or is currently distributed. Ibis does not have any plans to include any such Software in any such system or Product. The source code for all Software included in the Business IP is sufficiently documented such that a software programmer of ordinary skill would be able to maintain and modify such source code using reasonable efforts.

(xiv) Without limiting any other representation or warranty herein, the computer and other information technology systems and networks owned or contracted for by Ibis have been maintained in accordance with normal industry practice, are in good operating condition and repair (except for ordinary wear and tear) and are sufficient for the operation of the Business. Each of Ibis and Isis has taken all reasonably necessary action to safeguard the computer and other information technology systems and networks used in the operation of the Business and there has been no unauthorized intrusions or breaches of the security of the computer and other information technology systems and networks used in the Business that have materially compromised or are currently materially compromising the security, integrity or operations of such systems or networks.

(xv) The individuals identified as the outside counsel involved in the development or prosecution of the Business IP on Schedule 1(rr) represent the

outside counsel who have provided Isis or Ibis strategic legal and Intellectual Property advice related to the Business IP and the Ibis Business during the three (3) years prior to the Closing Date.

(m) Compliance with Other Instruments. Neither Ibis nor, with respect to the Business, Isis is in violation or default of any term of its charter documents, each as amended, or of any provision of any Contract to which it is party or by which the Business is bound or of any judgment, decree, order or writ.

(n) Litigation. There is no Claim pending or, to Isis' or Ibis' Knowledge, threatened against Ibis or, with respect to the Business, Isis (or against any Ibis or Isis employee (in their capacity as such)), at Law or in equity, or before or by any Governmental Authority, and to Isis' or Ibis' Knowledge, there is no reasonable basis for any of the foregoing. Neither Ibis nor, with respect to the Business, Isis is subject to any outstanding order, judgment, or decree issued by any Governmental Authority or any arbitrator. Neither Ibis nor any of its Affiliates has received any opinion or memorandum or advice from legal counsel to the effect that Ibis or the Business is or was exposed, from a legal standpoint, to any material liability.

(o) Tax Matters.

(i) Ibis has filed all required Tax Returns. All Taxes owed and due by Ibis have been paid. No claim has ever been made by an authority in any jurisdiction that Ibis is or may be subject to taxation by that jurisdiction. There are no Encumbrances on any of the assets used by Ibis that arose in connection with any failure (or alleged failure) to pay any Tax. Schedule 5.1(o)(i) contains a list of states, territories and jurisdictions (whether foreign or domestic) in which Ibis is required to file Tax Returns.

(ii) Ibis has withheld and paid all Taxes required to have been withheld and paid in connection with amounts paid or owing by Ibis to any employee, independent contractor, creditor, stockholder, or other third party, and all Forms W-2 and 1099 required with respect

thereto have been properly completed.

(iii) There is no dispute or claim concerning any Tax liability of Ibis either (A) claimed or raised by any Governmental Authority or (B) as to which Isis or Ibis has Knowledge.

(iv) Neither Ibis nor, with respect to the Business, Isis, has waived any statute of limitations in respect of Taxes or agreed to any extension of time with respect to a Tax assessment or deficiency.

(v) To Isis' or Ibis' Knowledge based in good faith on advice of Deloitte & Touche LLP, (A) Ibis and Isis are and will be members of the same consolidated group, as such term is defined by Treasury Regulation § 1.1502-1(h), with Isis being the common parent of such consolidated group for all taxable years through and including the Closing and (B) unless the provisions of the Code pertaining to filing Tax Returns as a consolidated group are amended prior to the Closing, Ibis and Isis will be eligible to file a consolidated Tax Return in lieu of separate Tax Returns with respect

to income Tax imposed by Chapter 1 of the Code for all taxable years through and including the Closing.

(vi) Ibis is not and will not at the Closing be a party to any oral or written Tax sharing agreements or arrangements.

(p) Employees.

(i) Neither Ibis nor, with respect to the Business, Isis, is party to any collective bargaining agreement. There is no labor union organizing activity pending or, to Isis' or Ibis' Knowledge, threatened with respect to Ibis. Each of Ibis and, with respect to the Business, Isis has complied with all applicable Laws relating to the employment of labor and, within the last five (5) years, neither Ibis nor Isis, with respect to the Business, has experienced any strike, work stoppage, lockout, grievance, unfair labor practice claim or other labor relation problem, including, without limitation, any written dispute with or Claim by former employees regarding termination and/or severance pay. To the Knowledge of Isis or Ibis, no executive, key employee or group of employees of Ibis has any plans to terminate employment with Ibis. In the past three (3) years, Ibis and Isis have complied in all respects with the notification provisions (or paid severance in lieu thereof) of the WARN Act and applicable similar state or local laws. No executive, key employee or group of employees of Ibis or the Business has been terminated or resigned their employment since the Investment Date.

(ii) Schedule 5.1(p)(ii) contains a true and complete list of each employment (other than at-will offer letters with no severance, compensation term guarantee or material benefit), bonus, fringe benefit, deferred compensation, incentive compensation, stock purchase, stock option, stock appreciation right or other stock-based incentive, severance, change-in-control, or other termination pay, hospitalization or other medical, disability, life or other insurance, supplemental unemployment benefits, profit-sharing, pension, or retirement plan, program or Contract and each other employee benefit plan, program or Contract sponsored, maintained or contributed to or required to be contributed to by Ibis, or by any trade or business, whether or not incorporated (an "ERISA Affiliate"), that together with Ibis or Isis would be deemed a "single employer" under Section 414(b), (c), (m) or (o) of the Code, for the benefit of any current or former employee or director of Ibis (the "Plans"). Schedule 5.1(p)(ii) identifies each Plan that is an "employee welfare benefit plan" or "employee pension benefit plan" as such terms are defined in Sections 3(1) and 3(2) of ERISA (such plans being hereinafter referred to collectively as the "ERISA Plans").

(iii) Except as specified in Section 8.11(d), neither Ibis nor Isis has any formal plan or binding commitment to create any additional Plan or modify or change any existing Plan that would affect any current or former employee or director of Ibis, except as required by Applicable Law or to conform such Plan to the requirements of any Applicable Law. Except for the Master Agreement and this Agreement, there are no Contracts or omissions that would prevent or impair any Plan (including any Plan covering retirees or other former employees) from being amended or terminated by Ibis or Isis prior to or at the Closing, or, with respect to the Plans listed on Schedule 5.1(p)(xii)

if any, by Ibis or AMI (or any successor thereto) on or at any time after the Closing.

(iv) Neither Isis nor Ibis has incurred and has no reason to expect that either will incur any liability to the Pension Benefit Guaranty Corporation (other than premium payments) or otherwise under Title IV of ERISA (including any withdrawal liability) or under the Code or any Applicable Law with respect to any employee pension benefit plan that Isis or Ibis, or any other entity that together with Isis or Ibis is treated as a single employer under Section 414 of the Code, maintains or ever has maintained or to which it contributes, ever has contributed, or ever has been required to contribute.

(v) Neither Ibis nor Isis, nor any of the ERISA Plans, nor any trust created thereunder, nor to Isis' or Ibis' Knowledge, any trustee or administrator thereof has engaged in a transaction or has taken or failed to take any action in connection with which Ibis could be subject to any material liability for either a civil penalty assessed pursuant to Sections 409 or 502(i) of ERISA or a tax imposed pursuant to Sections 4975, 4976 or 4980B of the Code.

(vi) Each Plan is in all material respects in compliance, and has been administered in all material respects in accordance, with the applicable provisions of ERISA, the Code and all other Applicable Laws, including, but not limited to, medical continuation under Section 4980B of the Code. Neither Isis nor Ibis has (A) engaged in any transaction prohibited by ERISA or the Code; (B) breached any fiduciary duty owed by it with respect to the Plans; or (C) failed to file and distribute timely and properly all reports and information required to be filed or distributed in accordance with ERISA or the Code.

(vii) Other than routine claims for benefits, there are no Claims, Internal Revenue Service or Department of Labor compliance programs or other proceedings pending or, to Isis' or Ibis' Knowledge, threatened against or otherwise involving any Plan.

(viii) Each Plan which is intended to be qualified under Section 401(a) of the Code (A) has been amended to reflect all requirements under the Code which are required to be adopted prior to the end of the applicable remedial amendment period and (B) has received from the Internal Revenue Service a favorable determination letter which considers the terms of the Plan as amended for such changes in Law.

(ix) None of the Plans obligates Isis or Ibis either (A) to pay any separation, severance, termination or similar benefit to Ibis Employees or (B) to make an excess parachute payment within the meaning of Code Section 280G.

(x) No Plan provides benefits, including without limitation death or medical benefits (whether or not insured), with respect to current or former employees of Ibis after retirement or other termination of service (other than (A) coverage mandated by any Applicable Law, (B) death benefits or retirement benefits

under any employee pension benefit plan or (C) benefits, the full direct cost of which are borne by the current or former employee (or beneficiary thereof)).

(xi) To Isis' or Ibis' Knowledge, other than as provided under the terms of the Plans, neither Ibis nor Isis has made any representation or commitment to, or entered into any formal or informal understanding with, any Ibis employee with respect to compensation, benefits, or terms of employment to be provided by AMI or Ibis or any of their respective Affiliates at or subsequent to the Closing.

(xii) Except for the Bonus Arrangement, Ibis neither sponsors nor maintains nor has any liability for (A) any of the Plans or (B) any other employee benefit plans or arrangements.

(xiii) All contributions, premiums or payments under or with respect to each Plan which are or were due have been paid.

(q) Compliance with Laws; Licenses.

(i) Ibis, the Business and, with respect to the Business, Isis are not in material violation of any Law. Ibis, the Business, and, with respect to the Business, Isis and Ibis' and Isis' Representatives have complied with, and are in material compliance with, all Applicable Laws, including, without limitation, the federal Food, Drug, and Cosmetic Act, as amended and regulations promulgated thereunder, and all U.S. Food and Drug Administration ("FDA") or its foreign equivalent regulations governing, among other things, the protection of human subjects and regulations governing clinical investigators. No governmental orders, permissions, consents, approvals or authorizations are required to be obtained and no registrations or declarations are required to be filed in connection with the execution and delivery of the Transaction Documents or the Transfer of the Remaining Shares.

(ii) Ibis holds all Licenses necessary for the operation or conduct of the Business (including pursuant to Environmental Laws). Schedule 5.1(q)(ii) sets forth a list of all Licenses material to the Business (the "Material Licenses"). Ibis is and has been in compliance with all terms and conditions of such Material Licenses and all Material Licenses may be relied upon by Ibis immediately following the Closing for the lawful operation of the Business as conducted on and prior to the date hereof. Each Material License is valid, binding and in full force and effect and Ibis and the Business have complied in all material respects with all requirements of and are not in default under any Material License and have not received written or, to Isis' or Ibis' Knowledge, oral notice that the Business or Ibis is in violation of any of the terms or conditions of such Material License. No loss or suspension of any License nor any proceeding or investigation which is seeking such a loss or suspension is pending or, to Isis' or Ibis' Knowledge, threatened. Neither Ibis nor Isis is operating under any written or oral formal or informal agreement or understanding with any licensing authority, Regulatory Authority or any other Governmental Authority which restricts the conduct of the Business or requires Ibis or, with respect to the Business, Isis, to take or refrain from taking any actions.

(r) Environment, Health and Safety. Ibis and the Business have at all times materially complied with and are in material compliance with all Environmental Laws, including, without limitation, all Licenses and other authorizations that are required pursuant to Environmental Laws for the ownership and occupation of the assets used by Ibis and the operation of the Business. Neither Ibis nor Isis, with respect to the Business is aware of or has reason to be aware of or has received any notice, request for information, report, order, directive, communication or other information, written or oral, regarding any actual or alleged violation of Environmental Laws, or any Claims or other liabilities or potential liabilities (whether accrued, absolute, contingent, unliquidated or otherwise) arising under Environmental Laws, relating to the Business, the Real Property or Ibis, which has not been resolved without liability to Ibis. Neither Ibis nor its Affiliates nor any of its legal predecessors has, in violation of Environmental Laws, treated, stored, disposed of, arranged for or permitted the disposal of, transported, handled, or Released, or exposed any Person to, any Hazardous Materials, or owned or operated any property or facility (and no such property or facility including the Real Property is contaminated by any such Hazardous Materials) so as to give rise to any current or future liability under Environmental Laws, including without limitation, any liability to investigate, remediate, cleanup, monitor or take any similar actions with respect to the environmental condition of any property (whether owned or non-owned), facility or treatment, storage or disposal facility. None of the following exists or to Isis' or Ibis' Knowledge, has ever existed at the Real Property: underground storage tanks, septic tanks, asbestos containing materials, polychlorinated biphenyls, lead-based paint, urea-formaldehyde, dumps, landfills, or waste disposal areas, sumps, pits, lagoons, surface impoundments or wetlands, or any contamination of any kind of the surface, subsurface, groundwater or surface water. Ibis has not assumed or become subject to, whether expressly or by operation of Law, any liabilities of any other Person arising under Environmental Laws or pursuant to any type of agreement. The consummation of the transactions contemplated by this Agreement do not impose any obligation on the Business under any Environmental Law or require notification to or consent of any Governmental Authority or third party pursuant to any Environmental Law. Ibis has provided to AMI copies of all material environmental Licenses, reports, audits, assessments, and investigations, and any other material environmental documents, relating to Ibis or the Business to the extent the foregoing are in the possession, custody, or control of Isis or any of its Affiliates or Ibis.

(s) Offering Valid. Assuming the accuracy of the representations and warranties of AMI contained in Section 5.2 hereof, the offer and sale of the Remaining Shares will be exempt from the registration requirements of the Securities Act, and will have been registered or qualified (or are exempt from registration and qualification) under the registration, permit or qualification requirements of all applicable state securities Laws. Neither Isis nor

any agent on its behalf has solicited or will solicit any offers to sell or has offered to sell or will offer to sell all or any part of the Remaining Shares to any Person or Persons so as to bring the sale of such Remaining Shares by Isis within the registration provisions of the Securities Act or any state securities Laws.

(t) Financial Statements.

(i) Schedule 5.1(t)(i) attached hereto contains the following financial statements (collectively the "Financial Statements"): (i) the profit and loss statement for the Division for the fiscal year ended December 31, 2007 and (ii) the profit

and loss statement for Ibis and the related balance sheet (the "Most Recent Balance Sheet") for the nine-month period ended September 30, 2008. The Financial Statements have been prepared in accordance with GAAP throughout the periods covered thereby, present fairly in all material respects the financial condition of Ibis or the Division (as the case may be) as of such dates and the results of operations of Ibis or the Division (as the case may be) for such periods, and are materially correct and complete and consistent with the books and records of Ibis (which books and records are materially correct and complete).

(ii) As of December 31, 2008, the [***], as determined in accordance with GAAP, on the Ibis balance sheet for the twelve-month period ending December 31, 2008 will be no less than $[***]. As of December 31, 2008, the [***], as determined in accordance with GAAP, on the Ibis balance sheet for the twelve-month period ending December 31, 2008 will be no more than $[***].

(u) Subsequent Events. Since the date of the Most Recent Balance Sheet, there has not been any material adverse change in the business, assets, liabilities, condition (financial or otherwise), operations, operating results, prospects, customer relations or supplier relations of Ibis and Ibis has and Isis has caused Ibis to conduct the Business in the ordinary course. Since the date of the Most Recent Balance Sheet:

(i) Ibis has not sold, leased, transferred, or assigned any of its assets to a third party, tangible or intangible, other than inventory in the ordinary course of business;

(ii) No party (including Ibis or Isis) has accelerated, terminated, modified, or canceled any material Contract (or series of related Contracts) to which Ibis is or was a party or by which the Business is or was bound;

(iii) Ibis has made capital expenditures consistent with its normal course of operations;

(iv) Ibis has not experienced any damage, destruction, or loss (whether or not covered by insurance) to its property over $50,000 in the aggregate;

(v) Ibis has not granted any increase in the base compensation of any employee, except in the ordinary course of business (including as to amount) or any bonus to, any employee, other than in the ordinary course of business;

(vi) Ibis has not amended, modified, or terminated any Plan (except as specified in Section 8.11(d));

(vii) Ibis has not entered into any transaction with any of its directors, officers, employees or Affiliates, except for transactions with its employees in the ordinary course of business;

(viii) Neither Ibis nor Isis has licensed, sublicensed, allowed any Encumbrance to exist on, abandoned, or permitted to lapse any Business IP or, except in

the ordinary course of business, disclosed any Confidential Information of Ibis or the Business to any Person (other than AMI and AMI's Representatives);

(ix) Ibis has not made a change in its accounting methods; and

(x) Ibis has not committed in any binding manner to any of the foregoing.

(v) Brokers' Fees. There are no brokerage commissions, finders' fees or similar compensation due in connection with the transactions contemplated by the Transaction Documents based on any arrangement or agreement made by or on behalf of Isis or Ibis. To the extent there are any brokerage commissions, finders' fees or similar compensation due in connection with the transactions contemplated by the Transaction Documents to [***] Isis shall be solely liable for any and all such amounts.

(w) Leased Real Property.

(i) Ibis does not own any real property and the ownership of any real property is not necessary for the operation of the Business. Ibis does not lease, sublease, license or otherwise grant any Person the right to use any real property. Neither Isis nor any of its Affiliates leases, subleases, licenses or occupies any real property used or occupied by, or necessary for the operation or conduct of, the Business.

(ii) Schedule 5.1(w)(ii) sets forth the names of the lessor and lessee, the address of each parcel of real property used by Ibis (collectively, the "Leased Real Property"), and a list of all leases, subleases, licenses and other agreements (whether written or oral) (collectively, "Leases") for each such Leased Real Property. None of the Leases is a ground lease. Ibis and Isis have delivered to AMI a true and complete copy of each such Lease document, and in the case of any oral Lease, a written summary of the material terms of such Lease. Ibis does not own any structures, improvements or fixtures located on any Leased Real Property (collectively, "Leasehold Improvements") and no Leasehold Improvements other than those provided to Ibis under the Corporate Services Agreement are material to the operation of the Business.

(iii) Each such Lease is legal, valid, binding, enforceable and in full force and effect.

(iv) Neither Ibis nor, to Isis' or Ibis' Knowledge, any other party to a Lease is in breach or default under such Lease, no event has occurred or circumstance exists which, with the delivery of notice, the passage of time or both, could reasonably be expected to constitute such a breach or default, or permit the termination, modification or acceleration of rent under such Lease and neither Ibis nor Isis has received notice that the Leased Real Property is in violation of any Applicable Law.

(v) No security deposit or portion thereof deposited with respect to such Lease has been applied in respect of a breach or default under such Lease which has not been redeposited in full. Neither Ibis nor any other Person owes any brokerage commissions, finder's fees, free rent or allowances with respect to such Lease.

(x) Contracts.

(i) Schedule 5.1(x)(i) lists the following Contracts relating to the Business or to which Ibis is a party: (A) Contract for the employment of any officer, individual employee, or other Person on a full-time, part-time, consulting, or other basis or Contract relating to loans to officers, directors, employees or Affiliates; (B) agreement or indenture relating to borrowed money or other Indebtedness or the mortgaging, pledging, or otherwise placing an Encumbrance on the assets or Capital Stock of Ibis; (C) lease or agreement under which Ibis is the lessee of or holds or operates any property, real or personal, owned by any other party, except for any lease or agreement for real or personal property under which the aggregate annual consideration is less than or equal to $25,000; (D) lease or agreement under which Ibis is the lessor of or permits any Person to hold or operate any property, real or personal, owned or controlled by Ibis; (E) distribution or franchise agreement; (F) agreement with a term of more than six months and (1) which is not terminable by Ibis upon less than 90 days' notice without penalty or (2) which involves aggregate annual consideration in excess of $25,000; (G) agreements relating to ownership of or investments in any business or enterprise, including joint ventures and minority equity investments; (H) Contract prohibiting it from freely engaging in any business or competing anywhere in the world; (I) except as otherwise disclosed on Schedule 5.1(x)(i) any other Contract or group of related Contracts with the same party or group of affiliated parties that involves aggregate annual consideration from or to Ibis in excess of $100,000; or (J) any Contract that is otherwise material to Ibis and/or the Business, including, without limitation, any IP Contract or Government Contract, whether or not entered into in the ordinary course of business and whether or not performance thereunder has been completed. All of the Contracts and other similar arrangements set forth on or required to be set forth on Schedule 5.1(x)(i) (the "Ibis Contracts").

(ii) All of the Ibis Contracts are valid, binding, enforceable and in full force and effect, and the transactions contemplated by the Transaction Documents will not cause such Contracts to cease to be valid, binding, enforceable and in full force and effect on identical terms following the Closing. Each of Isis or Ibis, as applicable, and, to Isis' or Ibis' Knowledge, each counterparty thereto has performed all material obligations required to be performed by it and is not in default under or in breach of or in receipt of any claim of default or breach under any Ibis Contract. No event has occurred which with the passage of time or the giving of notice or both would result in a default, breach or event of noncompliance by either Ibis or Isis or, to Isis' or Ibis' Knowledge, any other party under any such Ibis Contract. Neither Isis nor Ibis has received notice of the intention of any party to cancel or terminate any Ibis Contract and, to Isis' or Ibis' Knowledge, there has not been any breach or anticipated breach by the other parties to any such Ibis Contract.

(iii) Isis has provided AMI with a true and correct copy of all Ibis Contracts in each case together with all amendments, waivers, or other changes thereto (all of which are disclosed on Schedule 5.1(x)(i)). Schedule 5.1(x)(i) contains an accurate and complete description of all material terms of all oral Contracts referred to therein.

(y) Insurance. Schedule 5.1(y) attached hereto lists and briefly describes each insurance policy maintained by Ibis or Isis with respect to the Business (the "Insurance Policies"), together with a claims history for the past five (5) years for Ibis and, with respect to the Business, Isis. All of the Insurance Policies are in full force and effect, and neither Ibis nor Isis with respect to the Business is in default with respect to its obligations under any such insurance policy and neither Ibis nor Isis, with respect to the Business has been denied insurance coverage. Neither Ibis nor Isis, with respect to the Business has any self-insurance or co-insurance programs.

(z) Customers and Suppliers. Schedule 5.1(z) accurately sets forth a list of the Business' top ten customers by revenue for the fiscal year ended December 31, 2007 and the nine-month period ended September 30, 2008. Except as set forth on Schedule 5.1(z), neither Isis nor Ibis has received any indication from any material customer of the Business or any Governmental Authority to the effect that, and neither Isis nor Ibis has any reason to believe that, such customer or Governmental Authority will in the future stop, or materially decrease the rate of buying products or services from the Business. Schedule 5.1(z) also accurately sets forth a list of the Business' top ten suppliers by dollar amount for the nine-month period ended September 30, 2008. Except as set forth on Schedule 5.1(z), neither Isis nor Ibis has received any indication from any material supplier of the Business to the effect that, and neither Isis nor Ibis has any reason to believe that, such supplier will stop or materially decrease the rate of providing products or services to the Business and its customers. Neither Isis nor Ibis is involved in any material dispute with any customer or supplier of or to the Business.

(aa) No Material Adverse Effect. Since September 30, 2007, there has been no Material Adverse Effect.

(bb) Names and Locations. During the five-year period prior to the date hereof, neither Ibis nor the Business has used any name or names under which it has invoiced account debtors or maintained records concerning the assets used in the operation of the Business, other than Ibis Biosciences, Inc. and all of the assets used in the operation of the Business are located at the Leased Real Property.

(cc) Directors, Officers and Bank Accounts. Schedule 5.1(cc) (i) sets forth a true and correct list of the directors and officers of Ibis and the title of each such officer. Schedule 5.1(cc) (ii) lists all of Ibis' bank accounts, safety deposit boxes and lock boxes (designating each authorized signatory with respect thereto).

(dd) Regulatory Filings. Ibis and Isis have made available for inspection by AMI all material registrations, filings or submissions made with any Regulatory Authority or the SEC, and reports of audits ever issued by any Governmental Authority made by or with respect to Ibis or the Business. Ibis or Isis has timely filed, or caused to be timely filed, all material reports, statements, documents, registrations, filings or submissions required to be filed by Ibis or the Business with any Governmental Authority in connection with the operation of Ibis or the Business. All such registrations, filings and submissions are in material compliance in all respects with all Laws when filed or as amended or supplemented, and no deficiencies have been asserted by any such Governmental Authority with respect to such registrations, filings or submissions.

(ee) Disclosure. Neither the Transaction Documents, nor any of the Schedules delivered in connection herewith or therewith, contains any untrue statement of a material fact or omits a material fact necessary to make the statements contained herein or therein, in light of the circumstances in which they were made, not misleading. To Isis' or Ibis' Knowledge, there is no event, circumstance or other fact which Isis or Ibis has not disclosed to AMI in writing which has had or would reasonably be expected to have a Material Adverse Effect.

5.2 Representations and Warranties of AMI. As a material inducement to Isis to enter into this Agreement, AMI hereby represents and warrants to Isis that, except as set forth in the corresponding Section of the Disclosure Schedules, the following representations and warranties are as of the date hereof, and will be as of the Closing Date, true and correct:

(a) Power and Authority. AMI has the power, authority and the legal right to enter into the Transaction Documents and to perform its obligations hereunder and thereunder, and it has taken all necessary action required to authorize the execution and delivery of each such agreement and the performance of its obligations hereunder and thereunder.

(b) Enforceability. Each of the Transaction Documents has been duly executed and delivered on behalf of AMI and constitutes its legal, valid and binding obligation and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other Laws of general application affecting the enforcement of creditor rights.

(c) Governmental Authority; Consents. All necessary consents, approvals and authorizations of all Governmental Authorities and other parties required to be obtained by AMI in connection with the execution and delivery of the Transaction Documents and the performance of its obligations hereunder and thereunder have been obtained.

(d) No Conflicts. The execution and delivery of the Transaction Documents by AMI and the performance of its obligations hereunder and thereunder (i) do not conflict with or violate any requirement of Applicable Law or any provision of its certificate of incorporation or bylaws and (ii) do not require any notice, conflict with, violate, or breach or constitute a default or require any consent not already obtained or give rise to any termination or acceleration right under, any contractual obligation by which such Party is bound.

(e) Due Organization; Qualification. AMI is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to enter into the Transaction Documents and to perform its obligations hereunder and thereunder.

(f) Investment Representations. AMI understands that the Remaining Shares have not been registered under the Securities Act. AMI also understands that the Remaining Shares are being offered and sold pursuant to an exemption from registration contained in the Securities Act based in part upon AMI's representations contained in this Agreement. AMI hereby represents and warrants as follows:

(i) *AMI Bears Economic Risk.* AMI may be required to bear the economic risk of its investment in the Remaining Shares indefinitely unless the Remaining

Shares are registered pursuant to the Securities Act, or an exemption from registration is available.

(ii) *Acquisition for Own Account.* AMI is acquiring the Remaining Shares for AMI's own account for investment only, and not with a view towards their distribution.

(iii) *Accredited Investor.* AMI represents that it is an accredited investor within the meaning of Regulation D under the Securities Act.

(iv) *Ibis Information.* Ibis and Isis have given AMI an opportunity to discuss Ibis' business, management and financial affairs with directors, officers and management of Ibis and AMI has had an opportunity to review Ibis' operations and facilities.

(v) *Rule 144.* AMI acknowledges and agrees that the Remaining Shares are "restricted securities" as defined in Rule 144 promulgated under the Securities Act as in effect from time to time and must be held indefinitely unless they are subsequently registered under the Securities Act or an exemption from such registration is available. AMI has been advised or is aware of the provisions of Rule 144, which permits limited resale of shares purchased in a private placement subject to the satisfaction of certain conditions, including, among other things: the availability of certain current public information about Ibis, the resale occurring following the required holding period under Rule 144 and the number of shares being sold during any three-month period not exceeding specified limitations.

(g) Legends. AMI understands and agrees that the certificates evidencing the Remaining Shares will bear legends relating to restrictions on Transfer under federal and state securities Laws and legends required under applicable state securities Laws.

Section 6. RESERVED.

Section 7. PRE-CLOSING COVENANTS. The Parties agree as follows with respect to the period between the execution of this Agreement and the Closing:

7.1 General. Each of the Parties shall use its commercially reasonable efforts to take all action and to do all things necessary in order to consummate and make effective the transactions contemplated by this Agreement.

7.2 Affirmative Covenants of Isis and Ibis. Except as otherwise contemplated by this Agreement, between the date hereof and the Closing, each of Isis, with respect to the Business, and Ibis shall:

(a) conduct the Business only in the ordinary course; use commercially reasonable efforts to carry on the Business in the same manner as currently conducted and to keep Ibis' business organization and properties intact, including its business operations, physical facilities, working conditions, executives and key employees and Ibis' and the Business' relationships with lessors, licensors, suppliers, customers, carriers, consultants, independent contractors and others having business relations with Ibis or the Business;

(b) keep in full force and effect Ibis' organizational existence and all of its and the Business' assets, Contracts, rights, franchises, and Business IP and use commercially reasonable efforts to cause Ibis' and the Business' current insurance (or reinsurance) policies not to be canceled or terminated or any of the coverage thereunder to lapse;

(c) maintain the Real Property and other assets of Ibis (including the Business IP) in good repair, order and condition (normal wear and tear excepted) consistent with current needs, replace in accordance with prudent practices inoperable, worn out or obsolete assets with assets of good quality consistent with prudent practices and current needs and, in the event of a casualty, loss or damage to any of such assets or properties before the Closing Date, either repair or replace such damaged property or use the proceeds of such insurance in such other manner as mutually agreed upon by Isis and AMI; and

(d) maintain the books, accounts, and records of Ibis consistent with past practice and make capital expenditures at levels consistent with the past practices of Ibis and the Business.

7.3 Negative Covenants of Isis. Except as expressly contemplated by this Agreement or as set forth on Schedule 7.3, between the date hereof and the Closing, Ibis shall not and, with respect to Ibis and the Business, Isis shall not and shall cause Ibis not to:

(a) amend or waive any provision of Ibis' Certificate of Incorporation;

(b) take any action that would reasonably be expected to adversely affect the rights, preferences or privileges of the Shares, the Additional Shares or the Remaining Shares;

(c) take any action by written stockholder consent of Ibis without at least 2 Business Days prior written notice to AMI;

(d) redeem, repurchase, pay or declare dividends or other distributions with respect to any Capital Stock of Ibis;

(e) issue any Capital Stock of Ibis or any rights to acquire Capital Stock of Ibis;

(f) authorize or designate, whether by reclassification or otherwise, any new class or series of Capital Stock of Ibis or any increase in the authorized or designated number of any such class or series of Capital Stock of Ibis;

(g) enter into any transaction of merger, consolidation or sale of control, or liquidate, reorganize, recapitalize, wind up or dissolve Ibis, or Transfer any portion of Ibis' Capital Stock, properties, assets or business other than transfers of inventory in the ordinary course of business;

(h) sell, transfer, assign, license or sublicense, or allow any Encumbrance on any Business IP other than (i) rights of the U.S. federal government in Intellectual Property pursuant to the Government Contracts set forth on Schedule 5.1(l)(iii) or

new Government Contracts entered into in the ordinary course of business and (ii) end user license agreements related to the Software embodied in the T5000 Biosensor Systems that are issued in the ordinary course of business solely to purchasers of T5000 Biosensor Systems;

(i) abandon or permit to lapse any Business IP other than patents expiring at the end of their statutory terms (and not as a result of any act or omission by either Ibis or Isis, including, without limitation, a failure to pay any required maintenance fees) and limitations to the scope of claims of any pending patent application made during the ordinary course of prosecuting such pending patent applications;

(j) disclose any Confidential Information of the Business to any Person (other than AMI and its Representatives) other than in the ordinary course of business;

(k) create, incur, guarantee, assume, or be liable for any Indebtedness, other than Permitted Indebtedness in the ordinary course of business;

(l) subject any tangible asset of the Business to any Encumbrance, other than Permitted Encumbrances in the ordinary course of business and rights of the U.S. federal government in certain equipment purchased using government funds pursuant to (i) the Government Contracts set forth on Schedule 5.1(l)(iii) or (ii) new Government Contracts entered into in the ordinary course of business;

(m) (i) make any loan to or enter into any transaction with any officer, employee, partner or Affiliate, (ii) increase any officer's, employee's or partner's compensation outside the ordinary course of business, (iii) increase or accelerate any benefit, vesting schedule, obligation, subsidy or similar feature under any Plan outside the ordinary course of business, (iv) establish any Plan or (v) amend any Plan outside the ordinary course of business or commence making contributions to any multiemployer plan;

(n) make any acquisition, by means of merger, consolidation or otherwise, or any disposition, of assets or Capital Stock of any other Person;

(o) make any loans or capital contributions to, or investments in, any other Person, except advances to employees for reasonable expenses incurred in the ordinary course of business;

(p) enter into any Contract or amend any Contract required to be disclosed or to have been disclosed on Schedule 5.1(l) or Schedule 5.1(x), except in the ordinary course of business;

(q) enter into any strategic alliance, joint venture or joint marketing arrangement or agreement;

(r) delay or defer maintenance or repairs on any of Ibis' assets;

(s) waive or release any material Claim of Ibis;

(t) except as may be required by GAAP, make any material changes in policies or practices relating to selling practices, returns, discounts or other terms of the Business or accounting therefor, or in respect of the payment of trade payables or other similar liabilities incurred in connection with the operation of Ibis;

(u) increase or decrease marketing or promotional spending in any material respect from the rates established as of the date hereof, other than in the ordinary course of business;

(v) incur or guarantee any liability other than in connection with the performance or consummation of this Agreement;

(w) incur or commit to incur any capital expenditures in excess of $100,000 which would be payable after the Closing;

(x) take or omit to take any action that has or could reasonably be expected to have the effect of accelerating to pre-Closing periods sales that would otherwise be expected to occur after the Closing or otherwise in anticipation of the transactions contemplated hereby;

(y) take or omit to take any action that has or could reasonably be expected to have the effect of decelerating to post-Closing periods any payments or liabilities that would otherwise be expected to occur prior to the Closing or otherwise in anticipation of the transactions contemplated hereby;

(z) except as otherwise contemplated by this Agreement, pay, discharge, settle or satisfy any claim, liability or obligation or litigation (whether or not commenced prior to the date of this Agreement) outside the ordinary course of business;

(aa) take any other action which would reasonably be expected to interfere with, impede or materially delay the transactions contemplated hereby or dilute the benefits hereof to AMI and its Affiliates; or

(bb) commit, or enter into any agreement to do, any of the foregoing.

7.4 Notices and Consents. Each of the Parties will give any notices to, make any filings with and use its commercially reasonable efforts to obtain any authorizations, consents and approvals of third parties and Governmental Authorities in connection with the matters referred to in Sections 5.1(c) (Governmental Authority; Consents) and 5.1(d) (No Conflicts) above, including without limitation the transfers of Licenses.

7.5 Full Access. Ibis will cooperate with AMI in AMI's investigation of Ibis and the Business, and Ibis will permit AMI and its employees, agents, accountants, attorneys, environmental consultants, and other authorized representatives to (a) have full access to the premises, books and records of Ibis and, to the extent related to the Business, Isis, upon reasonable prior notice during normal business hours, (b) visit and inspect any of the properties of Ibis and, to the extent related to the Business, Isis, upon reasonable prior notice during normal

business hours and (c) discuss the affairs, finances and accounts of Ibis with the officers, directors, employees, key customers, suppliers and independent accountants of Ibis.

7.6 Transition Assistance. From and after the date hereof, neither Isis nor Ibis will in any manner take or cause to be taken any action which is designed, intended or might reasonably be anticipated to have the effect of discouraging current or potential customers, suppliers, licensors, lessors, independent contractors, consultants, employees and other associates of Ibis or the Business from establishing or maintaining the same business relationships with AMI after the date of this Agreement as were maintained with Ibis or the Business prior to the date of this Agreement.

7.7 Notice of Developments.

(a) Isis shall promptly (once Isis or Ibis obtains Knowledge thereof, but in any event within [***] of such Knowledge) inform AMI in writing of any inaccuracy in or breach of the representations and warranties contained in Section 5.1 or any breach of any covenant hereunder by Ibis or Isis. No such disclosure by Isis pursuant to this Section 7.7, however, shall be deemed to cure any breach of any representation or warranty or covenant

contained herein for purposes of determining the fulfillment of the conditions set forth in Sections 4.1(a) and 4.1(b) as of the Closing or for purposes of determining the liability of Isis with respect thereto under Section 8.2(a).

(b) AMI shall promptly (once AMI obtains Knowledge thereof, but in any event within three (3) Business Days of such Knowledge) inform Isis in writing of any inaccuracy in or breach of the representations and warranties contained in Section 5.2 or any breach of any covenant hereunder by AMI. No such disclosure by AMI pursuant to this Section 7.7, however, shall be deemed to cure any breach of any representation or warranty or covenant contained herein for purposes of determining the fulfillment of the conditions set forth in Sections 4.2(a) and 4.2(b) as of the Closing or for purposes of determining the accuracy of the representations and warranties contained in Section 5.2 and the liability of AMI with respect thereto under Section 8.2(c).

7.8 Exclusivity.

(a) Until the Closing, neither Isis, nor Ibis nor any of their respective Affiliates shall (and each shall (i) cause its Representatives and (ii) instruct its investment bankers, attorneys and accountants, not to), directly or indirectly, encourage, solicit, approve or recommend or participate in or initiate discussions or negotiations with, or provide any information to, any Person or group (other than AMI and its Representatives) concerning any Purchase Offer.

(b) Isis shall promptly, but in any event within [***], notify AMI of the existence of any attempted [***] by a non-intermediary principal received by Ibis or Isis or their respective Representatives, regarding any [***] and Ibis and Isis shall promptly, but in any event within [***], communicate to [***] which they may receive (and will immediately provide to AMI [***] and the [***]. Isis and Ibis shall promptly provide to AMI any [***] provided to any other Person by or on behalf of Ibis or Isis in connection with [***]

7.9 Indebtedness and Intercompany Accounts.

(a) Prior to the Closing, Isis (i) shall assume, extinguish, repay or contribute as equity, or shall cause to be assumed, extinguished, repaid or contributed as equity, all Indebtedness and ancillary obligations thereto owed by Ibis to any Person (including Isis and its Affiliates) (not including the amount of any Indebtedness that is Permitted Indebtedness under clauses (i) or (ii) of the Permitted Indebtedness definition that is owed to any Person other than Isis or any of its Affiliates), such that Ibis shall have no Indebtedness or ancillary obligations to any Person (not including the amount of any Indebtedness that is Permitted Indebtedness under clauses (i) or (ii) of the Permitted Indebtedness definition that is owed to any Person other than Isis or any of its Affiliates) and (ii) shall, and shall cause its Affiliates to, repay in full all Indebtedness and ancillary obligations thereto it or they owe to Ibis.

(b) Prior to the Closing, Isis shall, and shall cause its Affiliates to, settle or extinguish all intercompany receivables and payables that were incurred on or prior to the Closing and that arose from transactions between Isis or its Affiliates (other than Ibis), on the one hand, and Ibis, on the other hand.

(c) At the Closing, Isis shall cause to be delivered to AMI (i) the Remaining Shares free and clear of all Encumbrances, (ii) the assets of Ibis free and clear of all Encumbrances, other than Permitted Encumbrances and (iii) payoff letters with respect to any Indebtedness of Ibis to be paid by AMI at the Closing (in each case in form and substance reasonably satisfactory to AMI).

(d) At or prior to the Closing, Isis and Ibis shall (i) amend the Contribution Agreement as reasonably requested by AMI and (ii) terminate the Corporate Services Agreement and any other intercompany agreements and arrangements, except the Contribution Agreement (as amended under clause (i) above), the Transaction Documents and the arrangements expressly contemplated by the Transaction Documents.

7.10 Distribution of Cash.

Immediately prior to the Closing, Ibis may distribute to Isis all of its cash and cash equivalents in excess of the amount, not to exceed $[***], required to pay for [***] for which payment has not been made by Ibis prior to the Closing Date. Notwithstanding the foregoing, [***] will be distributed after the Closing in accordance with Section 8.14 [***].

7.11 [***] and [***].

Prior to the Closing Date, Ibis shall order, pay for and ensure the delivery to Ibis of, no fewer than [***] working [***] meeting the requirements set forth on Exhibit F attached hereto. In addition, Ibis shall order $[***] worth of the [***] set forth on Exhibit F that are necessary to manufacture [***] (the "[***]").

7.12 Permitted Indebtedness.

On or prior to the Closing Date, AMI shall, at AMI's option, either (a) execute and deliver to [***] a written [***] pursuant to which AMI [***], effective as of the Closing, Ibis'

[***], not to exceed $[***], under (i) that certain [***], by and between [***] and Ibis, and (ii) that certain related [***] issued by Ibis to [***] (the "[***]"), (b) consent to the transfer to Isis of the [***] attached to such [***] or (c) [***] the [***], including any [***].

7.13 Bonus Arrangement Payments.

On or prior to the Closing Date, Isis and Ibis shall satisfy all obligations under the Bonus Arrangement, including paying all amounts due thereunder to Ibis Employees.

Section 8. ADDITIONAL AGREEMENTS.

8.1 Survival. The covenants in this Agreement shall survive the Closing indefinitely, except as otherwise provided herein. The representations and warranties in this Agreement shall survive the Closing as follows:

(a) the Fundamental Isis Representations, other than the representations contained in Section 5.1(t)(ii), which shall terminate on the [***] anniversary of the Closing Date, and the Fundamental AMI Representations shall terminate on [***];

(b) the representations and warranties in Section 5.1(o) (Tax Matters), Section 5.1(p) (Employees) and Section 5.1(r) (Environment, Health and Safety) shall terminate [***] and the representations and warranties in Section 5.1(l) (Intellectual Property) shall terminate on the [***] anniversary of the Closing Date; and

(c) all other representations and warranties in this Agreement shall terminate on the [***] anniversary of the Closing Date.

Notwithstanding the foregoing, claims for indemnification pursuant to Section 8.2 as to which the Indemnified Party has given the Indemnifying Party proper notice pursuant to Section 10.6 prior to the expiration of the applicable survival period shall survive such expiration until such claims are resolved by written agreement of the Parties or by order of a court of competent jurisdiction.

8.2 Indemnification.

(a) Isis shall indemnify, defend and hold harmless AMI, Ibis, their respective officers, directors, shareholders, employees, representatives, agents and Affiliates (collectively, the "AMI Group") against any Losses which any of them may suffer, sustain, or become subject to, as a result of:

(i) the breach of any representation or warranty made by either Isis or Ibis in the Transaction Documents or in any certificate delivered by Isis or Ibis pursuant hereto or thereto;

(ii) the breach of any covenant or agreement made by either Isis or Ibis in the Transaction Documents or in any certificate delivered by Isis or Ibis pursuant hereto or thereto;

(iii) (A) any Plan of any entity that together with Ibis constitutes a controlled group of entities with Isis under Section 414(b), (c), (m) or (o) of the Code, (B) any former employee of Ibis or Isis who is not an Ibis Employee (regardless of when such Loss arises) and (C) any Ibis Employees, in each case, incurred on or prior to the Closing Date;

(iv) the conduct or operation of the Business or ownership or occupancy of the assets used in the Business on or prior to the Closing Date;

(v) the Bonus Arrangement;

(vi) any services provided to Ibis prior to the Closing Date [***], whether as an employee, independent consultant or otherwise, including the matters described in [***];

(vii) the matters described in [***] of the [***]; and

(viii) [***] claims from [***] related to goods and services provided to [***] by Ibis prior to the Closing pursuant to any Contract listed on Exhibit C to the extent such [***] claims are in excess of the [***].

(b) With respect to claims for indemnification pursuant to Sections 8.2(a)(i), 8.2(a)(iii) or 8.2(a)(iv) above, Isis will be liable to the AMI Group for any such Losses only if the aggregate amount of all such Losses relating to all such breaches exceeds [***], in which case Isis will be [***]. Notwithstanding the foregoing, the recovery limitations set forth in this Section 8.2(b) shall not apply to any Losses suffered as a result of the breach by Isis or Ibis of any [***].

(c) AMI shall indemnify, defend and hold harmless Isis, its respective officers, directors, shareholders, employees and Affiliates (the "Seller Group") against any Losses which any of them may suffer, sustain or become subject to, as the result of:

(i) the breach of any representation or warranty made by AMI in the Transaction Documents or in any certificate delivered by AMI pursuant hereto or thereto;

(ii) the breach of any covenant or agreement made by AMI in the Transaction Documents or in any certificate delivered by AMI pursuant hereto or thereto; and

(iii) the conduct or operation of the Business or ownership or occupancy of the assets used in the Business after the Closing Date.

(d) With respect to claims for indemnification pursuant to Sections 8.2(c)(i) and 8.2(c)(iii) above, AMI will be liable to the Seller Group for any such Losses only if the aggregate amount of all such Losses relating to all such breaches exceeds [***], in which case AMI will be [***]. Notwithstanding the foregoing, the recovery limitations set forth in this

Section 8.2(d) shall not apply to any Losses suffered as a result of the breach by AMI of any [***].

(e) If any third party shall notify any Party to this Agreement (the "Indemnified Party") of any matter which may give rise to a claim (a "Third Party Claim") for indemnification against any other Party to this Agreement (the "Indemnifying Party") under this Section 8.2, then the following procedures shall apply:

(i) The Indemnified Party shall notify the Indemnifying Party thereof; *provided*, that the failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party of its obligations hereunder except to the extent such failure shall have actually materially prejudiced the Indemnifying Party.

(ii) If the Third Party Claim pertains to any matter other than those identified in Sections 8.2(a)(vi) or 8.2(a)(vii), once the Indemnified Party has given notice of the matter to the Indemnifying Party, the Indemnified Party shall defend against the matter in any manner it reasonably may deem appropriate. The Indemnifying Party may, at its sole cost and expense, participate in the defense of such Claim with co-counsel of its choice. Notwithstanding the foregoing or any other provision in this Agreement to the contrary, the Indemnifying Party shall not have the right to participate in such defense if the claim in which the Indemnifying Party seeks to participate (A) seeks non-monetary relief that does not seek to obtain a license or other access to, restrict the scope of, or adversely affect the enforceability of, any Intellectual Property controlled by the Indemnifying Party, (B) seeks injunctive relief, (C) involves criminal allegations against an Indemnified Party or (D) is one in which the Indemnifying Party is also a party and joint representation would be inappropriate or there may be legal defenses available to the Indemnified Party which are different from or additional to those available to the Indemnifying Party. The Indemnified Party shall not consent to the entry of any judgment with respect to the matter or enter into any settlement with respect to the matter without the Indemnifying Party's prior written consent (not to be unreasonably withheld, conditioned or delayed).

(iii) If the Third Party Claim pertains to any matter identified in Sections 8.2(a)(vi) or 8.2(a)(vii), in connection with the prosecution, defense and resolution of such matter, as among Isis and the members of the AMI Group, once a member of the AMI Group has given notice of the matter to Isis, Isis shall control the prosecution, defense and resolution of such matter as it may reasonably deem appropriate. Notwithstanding the foregoing or any other provision in this Agreement to the contrary (A) the AMI Group will have the right to participate, at its own expense, in the prosecution, defense or resolution of such Third Party Claim to the extent such Third Party Claim (1) seeks injunctive relief against a member of the AMI Group, (2) involves criminal allegations against a member of the AMI Group or (3) is one in which Isis is also a party and joint representation would be inappropriate or there may be legal defenses available to a member of the AMI Group which are different from or additional to those available to Isis (such Third Party Claims, to the extent meeting the criteria set forth in subsections (e)(iii)(A)(1), (e)(iii)(A)(2) or (e)(iii)(A)(3) above are referred to as "Special AMI Claims"), (B) Isis shall not consent to the entry of any judgment with

respect to any matter identified in Sections 8.2(a)(vi) or 8.2(a)(vii) or enter into any settlement with respect to such matter without AMI's prior written consent (not to be unreasonably withheld, conditioned or delayed), (C) the AMI Group shall not consent to the entry of any judgment with respect to any Special AMI Claims or enter into any settlement with respect to such Special AMI Claims without Isis' prior written consent (not to be unreasonably withheld, conditioned or delayed) and (D) for any matter that Isis is entitled to control pursuant to this Section 8.2(e)(iii), Isis shall promptly advise in-house counsel designated by AMI of all court filings as well as developments with respect to such matter.

(f) None of the AMI Group or the Seller Group shall be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that any such Person has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including but not limited to the earnout payment reductions provided under Sections 2.3(a) and 2.3(b)) or the Master Agreement, it being understood and agreed that application of the foregoing provision shall not preclude the AMI Group from recovering any Losses incurred by the AMI Group in connection with the operation of the Business or the exploitation of the Business IP that are not [***].

(g) In determining (i) whether any representation, warranty, covenant or agreement contained herein has been breached or (ii) the amount of any Loss with respect thereto, any materiality, Material Adverse Effect, or similar qualification contained therein shall be disregarded.

(h) Indemnification for each Loss for which an Indemnifying Party, but for this Section 8.2(h), would be liable under Section 8.2(a) or Section 8.2(c) shall be reduced by the amount of any insurance proceeds actually paid to any member of the AMI Group or the Seller Group, as the case may be, by any unaffiliated third party with respect to such Loss, in each case net of any Losses incurred by any member of the AMI Group or the Seller Group as the case may be in collecting such proceeds or payments; *provided* that this Section 8.2(h) shall not limit in any respect the right of any member of the AMI Group or the Seller Group, as the case may be, to pursue indemnification from an Indemnifying Party hereunder or from recovering for any Loss not reduced to zero pursuant to this Section 8.2(h). Nothing contained herein shall be deemed to cause any amounts for which a member of the AMI Group or the Seller Group, as the case may be, would ultimately be responsible, as a result of deductibles, self-insurance, indemnification of insurers, caps or similar items or arrangements, to not be subject to indemnification as "Losses" hereunder.

(i) For Tax purposes, the Parties agree to treat all payments made under this Section 8.2 as adjustments to the Purchase Price, except to the extent any applicable Tax Law does not permit such treatment. If any Governmental Authority disputes treatment as an adjustment to the Purchase Price, the Party receiving notice of such dispute will promptly notify and consult the other Party concerning resolution of such dispute.

8.3 Press Release and Announcements. On the date hereof, the Parties may issue a press release announcing the execution of this Agreement, substantially in the form attached hereto as Exhibit G. Each Party agrees not to issue any other press release or other

public statement relating to or make any public filing with respect to the Transaction Documents or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed. Each Party agrees to provide to the other Party a copy of any public announcement or public filing regarding the Transaction Documents or the subject matter thereof as far in advance as 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 [***] prior to its scheduled release. The contents of any announcement or filing or similar publicity which has been reviewed, approved and released by the reviewing Party may be re-released by either Party without a requirement for advance notice or re-approval.

8.4 Expenses. Except as otherwise provided herein, each of AMI and Isis will bear its own costs and expenses (including, without limitation, all legal, accounting, consulting, investment banking, brokerage and other fees and expenses) incurred in connection with this Agreement and the transactions contemplated hereby; provided that all costs and expenses associated with obtaining third party consents with respect to Ibis Contracts or any Restricted Asset less than or equal to [***] in the aggregate shall be borne by AMI and that, in accordance with Section 2.5, all such costs and expenses in excess of [***] in the aggregate shall be borne by Isis; provided further, that the initial premerger notification and filing fee for HSR shall be borne by AMI, but any fees arising from any subsequent filings with respect thereto shall be borne equally by AMI and Isis.

8.5 Setoff. AMI and Ibis shall have the right to set off any claim AMI or Ibis may have against Isis under this Agreement or the Transition Services Agreement against any amounts owing to Isis under this Agreement; provided that (i) AMI provides written notice to Isis of such setoff claim and (ii) initiates the ADR process described in Exhibit H hereto. AMI shall setoff any amounts pursuant to the foregoing by [***]

8.6 Certain Tax Matters.

(a) Transfer Taxes. All transfer, sales, use, stamp, registration and such Taxes and fees (including any penalties, interest and filing expenses) incurred in connection with this Agreement shall be paid by Isis, and Isis will prepare and file all necessary Tax Returns and other documentation with respect to all such transfer, documentary, sales, use, stamp, registration and other taxes and fees, and, if required by applicable law, the Parties will, and will cause their Affiliates to, cooperate in the execution of such Tax Returns. If AMI or one of its Affiliates is required to execute any Tax Return prepared by Isis under this section, Isis will provide a copy of such Tax Return to AMI at least 10 days prior to the anticipated filing of such Tax Return and AMI or its Affiliate shall execute the Tax Return, subject to Abbott's reasonable approval.

(b) Ad Valorem Taxes. All real property Taxes, personal property Taxes, ad valorem obligations and similar Taxes imposed on a periodic basis, in each case levied on Ibis, other than transfer Taxes provided for in Section 8.6(a) above, for a taxable period which includes (but does not end on) the Closing Date shall be apportioned between Isis and AMI as of the Closing Date based on the number of days of such taxable period included in the Pre-Closing Tax period and the number of days of such taxable period included in the Post-Closing period. Isis shall be liable for the proportionate amount of such Taxes that is attributable to the

Pre-Closing Tax period. Within 90 days after the Closing, Isis and AMI shall present a reimbursement to which each is entitled under this Section 8.6(b) together with such supporting evidence as is reasonably necessary to calculate the proration amount; *provided*, that if the final Tax amount due for a taxable period that includes the Closing Date is not determined within such period, a reimbursement shall be based on the amount of the relevant Tax for the preceding taxable year, subject to an adjustment within 30 days after the final amount of such Tax is determined. The proration amount shall be paid by the Party owing it to the other within 10 days after delivery of such statement. Thereafter, Isis shall notify AMI upon receipt of any bill for real or personal property Taxes relating to Ibis, part or all of which are attributable to the Post-Closing Tax period, and shall promptly deliver such bill to AMI who shall pay the same to the appropriate taxing authority, *provided*, that if such bill covers any portion of the Pre-Closing Tax period, Isis shall also remit prior to the due date of assessment to AMI payment for the proportionate amount of such bill that is attributable to the Pre-Closing Tax period. In the event that either Isis or AMI shall thereafter make a payment for which it is entitled to reimbursement under this Section 8.6(b), the other Party shall make such reimbursement promptly but in no event later than 30 days after the presentation of a statement setting forth the amount of reimbursement to which the presenting Party is entitled along with such supporting evidence as is reasonably necessary to calculate the amount of reimbursement. Any payment required under this Section 8.6(b) and not made within 10 days of delivery of the statement shall bear interest at the Applicable Rate for each day until paid.

(c) Tax Liability.

(i) Isis shall, in accordance with Section 8.2(a) (except as explicitly provided in this Section 8.6), indemnify and hold harmless the AMI Group from any and all Losses arising from: (1) all Taxes (or the non-payment thereof) of Ibis for the Pre-Closing Tax Period, (2) all Taxes of any member of an affiliated, consolidated, combined or unitary group of which Ibis (or any predecessor thereof) is or was a member on or prior to the Closing Date, including pursuant to U.S. Treasury Regulation §1.1502-6 or any analogous or similar state, local, or foreign Law, and (3) any and all Taxes of any Person (other than Ibis) imposed on Ibis as a transferee or successor, by contract or pursuant to any Law, which Taxes relate to an event or transaction occurring before the Closing.

(ii) To the extent there is any taxable period that includes (but does not end on) the Closing Date (a "Straddle Period"), the amount of any Taxes based on or measured by income or receipts of Ibis for the Pre-Closing Tax Period shall be determined based on an interim closing of the books as of the close of business on the Closing Date (and for such purpose, the taxable period of any partnership or other pass-through entity in which Ibis holds a beneficial interest shall be deemed to terminate at such time) and the amount of other Taxes of Ibis for a Straddle Period that relates to the Pre-Closing Tax Period shall be deemed to be the amount of such Tax for the entire taxable period multiplied by a fraction the numerator of which is the number of days in the taxable period ending on the Closing Date and the denominator of which is the number of days in such Straddle Period.

(iii) AMI shall, in accordance with Section 8.2(c) (except as explicitly provided in this Section 8.6), indemnify and hold harmless the Seller Group from any and all Losses arising from: (1) all Taxes (or the non-payment thereof) of Ibis for the Post-Closing Tax Period, (2) all Taxes of any member of an affiliated, consolidated, combined or unitary group of which Ibis (or any successor thereto) is a member after the Closing Date, including pursuant to U.S. Treasury Regulation §1.1502-6 or any analogous or similar state, local, or foreign Law, and (3) any and all Taxes of any Person (other than Ibis) imposed on Ibis as a transferee or successor, by contract or pursuant to any Law, which Taxes relate to an event or transaction occurring after the Closing.

(iv) Isis' and AMI's obligations to indemnify for any Taxes under this Section 8.6 shall survive the Closing hereunder and continue until 30 days following the expiration of the statute of limitations on assessment of the relevant Tax. Notwithstanding the foregoing, any claim for indemnification shall survive such termination date if the Indemnified Party, prior to such termination date, shall have advised the Indemnifying Party in writing of facts that constitute or may give rise to an alleged claim for indemnification under this Section 8.6.

(d) Tax Returns.

(i) Isis shall file or cause to be filed when due (taking into account any extensions received from the relevant Tax authorities) (1) all Tax Returns that are required to be filed with respect to Ibis on or before the Closing Date, and (2) all Tax Returns that are required to be filed after the Closing Date with respect to income Taxes of Ibis with respect to all Pre-Closing Tax Periods, and shall pay when due (X) any income Taxes due in respect of such Tax Returns, and (Y) any other Taxes due in respect of such Tax Returns that are due on or before the Closing Date.

(e) Contest Provisions.

(i) Isis shall have the sole right to control the conduct and resolution of any audit, litigation, contest, dispute, negotiation, or other proceeding with any Tax authority that relates to income Taxes of Ibis relating to a Pre-Closing Tax Period, including, without limitation, by selecting counsel of its choice to represent Ibis, unless Isis fails to assert such control within 30 days of receiving notice of such proceeding (each such proceeding for which Isis asserts such control, an "Isis Proceeding"); *provided*, that (A) Isis shall consult with AMI and keep AMI informed regarding the progress and any potential compromise or settlement of each Isis Proceeding; and (B) AMI shall be entitled to participate at its own expense in each Isis Proceeding and (C) Isis shall not settle or otherwise compromise any Isis Proceeding without the consent of AMI to the extent such settlement or compromise would have an adverse effect on AMI or Ibis with respect to a Post-Closing Tax Period, which consent shall not be unreasonably withheld, conditioned or delayed.

(ii) AMI shall have the sole right to control the conduct and resolution of any audit, litigation, contest, dispute, negotiation, or other proceeding with

any Tax authority relating to Taxes of Ibis that is not an Isis Proceeding, including, without limitation, by selecting counsel of its choice to represent Ibis (each such proceeding, an "AMI Proceeding"); *provided*, that (A) AMI shall consult with Isis regarding the progress and any potential compromise or settlement of any Isis Proceeding that relates to Taxes for which Isis may be liable pursuant to Section 8.6(c)(i) of this Agreement (an "Applicable AMI Proceeding"); (B) Isis shall be entitled to participate at its own expense in any Applicable AMI Proceeding; and (C) AMI shall not settle or otherwise compromise any Applicable AMI Proceeding without the consent of Isis to the extent such settlement or compromise would have an adverse effect on Isis or Ibis with respect to a Pre-Closing Tax Period, which consent shall not be unreasonably withheld, conditioned or delayed.

(iii) Provided AMI fails to assert control over an Applicable AMI Proceeding within 30 days of receiving notice of such proceeding, Isis shall have the sole right to control the conduct and resolution of an Applicable AMI Proceeding with any Tax authority, including, without limitation, by selecting counsel of its choice to represent Ibis; *provided*, that (A) Isis shall promptly consult with AMI regarding the progress and any potential compromise or settlement of any Applicable AMI Proceeding; (B) AMI shall be entitled to participate at its own expense in any Applicable Isis Proceeding; and (C) neither Isis nor Ibis shall settle or compromise any Applicable AMI Proceeding without the prior written consent of AMI, which shall not be unreasonably withheld, conditioned or delayed.

(f) Assistance and Cooperation. From and after the Closing Date, each of Isis and AMI shall:

(i) assist (and cause their respective Affiliates to assist) the other party in preparing any Tax Returns which such other party is responsible for preparing and filing in accordance with this Section 8.6;

(ii) cooperate fully in preparing for any audit, litigation, contest, dispute, negotiation, or other proceeding with any Tax authority regarding Taxes of Ibis;

(iii) make available to the other party and to any Tax authority, as reasonably requested, all information, records, and documents relating to Taxes or Tax Returns of Ibis (including, without limitation, information necessary to file extensions and make estimated Tax payments); and

(iv) furnish the other party with copies of all correspondence received from any Tax authority in connection with any applicable Isis Proceeding or AMI Proceeding.

(g) Code § 338(h)(10) Election. At AMI's option, Isis and AMI shall join in making an election under Code § 338(h)(10) (and any corresponding elections under state, local, or foreign tax law) (collectively a "§ 338(h)(10) Election") with respect to the purchase and sale of the Shares, the Additional Shares and the Remaining Shares, unless and to the extent

the Code is amended to prevent or limit the filing of a § 338(h)(10) Election. Isis will pay any Tax attributable to the making of the § 338(h)(10) Election and will indemnify the AMI Group against any Losses arising out of any failure to pay such Tax.

(h) Allocation of Purchase Price. The Parties agree that the Purchase Price and the liabilities of Ibis (and other relevant items) will be allocated for tax purposes to the assets of Ibis in a manner consistent with Code §§ 338 and 1060 and the regulations thereunder. AMI, Ibis and Isis shall file all Tax Returns (including amended returns and claims for refund) and information reports in a manner consistent with such allocation.

8.7 Further Assurances. Isis will execute and deliver such further instruments of conveyance and transfer and take such additional action as AMI may reasonably request to effect, consummate, confirm or evidence the transfer to AMI of the Remaining Shares and the assets of the Business (including the Business IP and the Ibis Contracts), and Isis will execute such documents as may be necessary to assist AMI in preserving or perfecting its rights in the Shares, the Remaining Shares and the Business. Except for the services, funding and facilities provided under the Corporate Services Agreement, to the extent any assets used in the Business on or prior to the Closing Date (including the Business IP and the Ibis Contracts) or necessary to

conduct the Business as conducted on and prior to the Closing Date (including the Business IP and the Ibis Contracts) or as contemplated to be conducted after the Closing Date have not been duly and fully transferred to Ibis as of such date, Isis hereby covenants, at its sole cost and expense and without further consideration by AMI, to take all such actions as may be requested by AMI to promptly transfer such assets to Ibis or AMI's designee.

8.8 Confidentiality.

(a) Each Party agrees that for a period of three (3) years after the Closing Date, a Party (the "Receiving Party") receiving or that has received Confidential Information of the other Party (the "Disclosing Party") will (i) maintain and cause its Representatives to maintain in confidence such Confidential Information using not less than the efforts such Receiving Party uses to maintain in confidence other proprietary information of similar kind and value (it being understood and agreed that AMI shall have no obligation to maintain the confidentiality of any Ibis Confidential Information and that Isis shall have an obligation to maintain the confidentiality of all Ibis Confidential Information pursuant to this Section 8.8), (ii) not disclose such Confidential Information except to the Receiving Party's employees or Affiliates having a need-to-know such Confidential Information solely for purposes of performing the Receiving Party's obligations under the Transaction Documents, (iii) not disclose such Confidential Information to any Person without the prior written consent of the Disclosing Party, except for disclosures expressly permitted by the Transaction Documents, and (iv) not use such Confidential Information for any purpose except those expressly permitted by the Transaction Documents. The provisions of this Section 8.8 shall supersede the provisions of Section 5.1, Section 5.2 and Section 5.3 of the Master Agreement which shall terminate and be of no further force or effect from and after the Closing Date. Upon AMI's request Isis will return or destroy (and certify to AMI any such destruction) all Confidential Information of AMI or its Affiliates and upon Isis' request, AMI will return or destroy (and certify to Isis any such destruction) all Confidential Information of Isis that is not Confidential Information of Ibis;

provided, that AMI may retain one (1) copy of Isis' Confidential Information in Abbott's confidential files.

(b) To the extent (and only to the extent) that it is reasonably necessary, a Party may disclose Confidential Information belonging to the other Party in the following instances:

(i) when defending litigation related to the Confidential Information to be disclosed;

(ii) when complying with Applicable Laws (including, without limitation, the rules and regulations of the SEC or any national securities exchange, and compliance with Tax Laws) and with judicial process; and

(iii) disclosure, in connection with the performance of the Transaction Documents and solely on a need-to-know basis, to employees or independent contractors (including without limitation consultants and clinical investigators), each of whom prior to disclosure must be bound by written obligations of confidentiality and non-use no less restrictive than the obligations set forth in this Section 8.8; *provided*, that the Receiving Party will remain responsible for any failure by any Person who receives Confidential Information pursuant to this Section 8.8 to treat such Confidential Information as required under this Section 8.8.

(c) If and whenever any Confidential Information is disclosed in accordance with this Section 8.8, such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such permitted disclosure results in a public disclosure of such information (other than by breach of this Agreement). Except as prohibited by Law, the Receiving Party will notify the Disclosing Party of the Receiving Party's intent to make such disclosure pursuant to clauses (i) or (ii) of Section 8.8(b) sufficiently prior to making such disclosure so as to allow the Disclosing Party adequate time to take whatever action the Disclosing Party may deem appropriate to protect the confidentiality of the information. In addition, in the event any Party proposes to file with any Governmental Authority a Transaction Document, including, without limitation, as an exhibit to a registration statement, periodic report, or current report, the Party proposing to make such filing will notify the other Parties of such intention and will work in good faith with the other Parties to obtain confidential treatment of any material terms of the Transaction Documents that such other Parties request be kept confidential (except to the extent advised by counsel or such Governmental Authority that confidential treatment is not available for such information).

(d) At the Closing, Isis shall deliver to AMI all Confidential Information of the Business in Isis' or its Affiliates' possession and control and all copies thereof, in whatever form or medium, including, without limitation, written records, optical and magnetic media, and all other materials containing any such Confidential Information. If AMI requests, Isis shall promptly provide written confirmation that all such materials have been delivered to AMI.

(e) The existence and the terms and conditions of the Transaction Documents that the Parties have not specifically agreed to disclose pursuant to Section 8.8(b) or Section 8.3 will be considered Confidential Information of both Parties. AMI and, subject to the terms of Section 7.8, Isis may disclose such terms to a bona fide potential investor, investment banker, acquirer, merger partner or other potential business partner of AMI or Isis, respectively, and their attorneys and agents, *provided*, that each such Person to whom such information is to be disclosed is informed of the confidential nature of such information and has entered into a written agreement with the Party requiring such Person to keep such information confidential.

8.9 Noncompetition and Nonsolicitation. The Parties hereby agree as follows:

(a) Noncompetition. During the period from the date hereof to and including the [***] anniversary of the Closing Date (the "Noncompete Period"), Isis and its Affiliates shall not engage in and shall not have any affiliation with any Person that engages in a line of business that competes with the Business as conducted on and prior to the Closing Date and as contemplated by Ibis and Isis to be conducted after the Closing Date, as reflected in the Offering Memorandum and the Management Presentations. For purposes of this Section 8.9, the term "affiliation" shall mean any direct or indirect interest in such Person or enterprise, whether as an investor, partner, stockholder, operator, lender, trustee, joint venture contributor, licensor or consultant (other than passive investments by Isis of less than [***] of the outstanding equity securities of any entity listed for trading on a national stock exchange or investments in less than [***] of the outstanding equity securities by Isis in a Person engaged in drug discovery, development or commercialization).

(b) Pre-Existing Business. Notwithstanding the foregoing, if a Person becomes an Affiliate of Isis after the Closing Date, and such Person was engaged in a line of business that on or before the time such Person became an Affiliate of Isis, competed with the Business as conducted on and prior to the Closing Date and as contemplated by Ibis and Isis to be conducted after the Closing Date, as reflected in the Offering Memorandum and Management Presentations (a "Pre-Existing Business"), then the provisions of Section 8.9(a) will not apply to such Pre-Existing Business if (i) such third party does not [***] and (ii) appropriate protective measures and procedures are established by Isis and its Affiliates and such Person and its Affiliates to protect and safeguard the confidentiality of Abbott and Ibis Confidential Information.

(c) No Solicitation of AMI Employees. During the period from the date hereof to and including the [***] anniversary of the Closing Date (the "Nonsolicitation Period"), Isis (and until the Closing, Ibis) shall not and shall not permit any of their respective Representatives to directly or indirectly, (i) without the prior written consent of AMI, induce or attempt to induce any employee of AMI or any member of the Abbott Transaction Team to leave the employ of AMI or the applicable Abbott Affiliate, or in any way interfere with the relationship between AMI or the applicable Abbott Affiliates and any employee of AMI or any member of the Abbott Transaction Team, or Known consultant or independent contractor thereof or (ii) without the prior written consent of AMI, hire directly or through another entity any employee of AMI or any member of the Abbott Transaction Team or any Person who was an employee of AMI or a member of the Abbott Transaction Team who was employed by Abbott or

any of its Affiliates during the [***] months prior to the date of such hiring, in each case to work for Isis or Ibis.

(d) No Solicitation of Ibis or Isis Employees. During the Nonsolicitation Period with respect to employees of Isis and until the Closing with respect to employees of Ibis, AMI and its Affiliates will cause AMI and the members of the Abbott Transaction Team not to, directly or indirectly, (i) without the prior written consent of Isis or Ibis (as the case may be), induce or attempt to induce any employee of Isis or Ibis to leave the employ of Isis or Ibis, or in any way interfere with the relationship between Isis or Ibis and any of their respective employees, or Known consultant or independent contractor thereof or (ii) without the prior written consent of Isis or Ibis (as the case may be), hire directly or through another entity any employee of Isis or Ibis or any Person who was an employee of Isis or Ibis who was employed by Isis or Ibis during the [***] months prior to the date of such hiring, in each case to work for AMI.

(e) No Solicitation of Ibis Employees. During the Nonsolicitation Period, Isis shall not and shall not permit any of its Representatives to directly or indirectly (i) without the prior written consent of AMI, induce or attempt to induce any employee of Ibis to leave the employ of Ibis, or in any way interfere with the relationship between Ibis and any employee, consultant or independent contractor thereof, (ii) without the prior written consent of AMI, hire directly or through another entity any employee of Ibis or any Person who was an employee of Ibis during the [***] months prior to the date of such hiring or (iii) induce or attempt to induce any customer, supplier, licensee, licensor or other business relation of Ibis, AMI or any of their respective Affiliates or the Business, to cease doing business with Ibis, AMI or any of their respective Affiliates or the Business.

For purposes of Sections 8.9(c), 8.9(d) and 8.9(e), "recruit," "solicit" or "induce" shall not be deemed to mean (i) circumstances where an employee, consultant or independent contractor or former employee, consultant or independent contractor initiates contact with a Party with regard to possible employment, or (ii) general solicitations of employment not specifically targeted at specific employees of a Party, including responses to general advertisements.

Notwithstanding anything in this Section 8.9 to the contrary, if at any time a court holds that the restrictions stated in Section 8.9(a), Section 8.9(c), Section 8.9(d) or Section 8.9(e) or any part of any of the foregoing are unreasonable or otherwise unenforceable under circumstances then existing, the Parties hereto agree that the maximum period, scope or geographical area determined to be reasonable under such circumstances by such court will be substituted for the stated period, scope or area. The Parties acknowledge and agree that money damages may not be an adequate remedy for any breach or threatened breach of the provisions of Section 8.9(a), Section 8.9(c), Section 8.9(d) or Section 8.9(e) and that, in such event, any Party or its successors or assigns may, in addition to any other rights and remedies existing in its or their favor, apply to any court of competent jurisdiction for specific performance, injunctive and/or other relief in order to enforce or prevent any violations of the provisions of this Section 8.9 (including, if the court so determines, the extension of the Noncompete Period or the Nonsolicitation Period, as applicable, by a period equal to the length of court proceedings necessary to stop such violation). Any injunction shall be available without the posting of any bond or other security. In the event of an alleged breach or violation by any Party or any of their respective Representatives of any of

the provisions of this Section 8.9, the Noncompete Period or the Nonsolicitation Period, as applicable will be tolled until such alleged breach or violation is resolved. The Parties agree that the restrictions contained in this Section 8.9 are reasonable in all respects.

8.10 Access to Books and Records. After the Closing, Isis will permit AMI and its representatives, and AMI will permit Isis and its representatives, to have reasonable access upon prior notice and at reasonable times, and in a manner so as not to interfere with the normal business operations of the other Party, to all books, records (including Tax records), contracts and documents of or pertaining to Ibis.

8.11 Employee and Related Matters.

(a) Ibis Employees. All employees of Ibis employed as of the Closing Date (the "Ibis Employees") shall, as of the Closing, receive compensation and benefits from Abbott that are substantially comparable, in the aggregate, to the compensation and benefits received by other similarly-situated employees of Abbott based on Abbott's evaluation of the nature and scope of such employee's duties, principal location where those duties are performed, grade level and performance. To facilitate Abbott's obligations to provide such compensation and benefits under this Section 8.11, Isis shall provide AMI promptly, upon AMI's request, but in any event, no less than [***] prior to the Closing Date (and again on the Closing Date) a true, complete and accurate list of each Ibis Employee, including the date of employment and title or job position of each Ibis Employee, information regarding pay and benefits, including, but not limited to, the total annual salary, wages, bonus or other compensation of each Ibis Employee, and, with respect to any Ibis Employees who are inactive Ibis Employees (as defined in Section 8.11(f)), the date such inactive employee changed from active to inactive status, the reason for such inactive status and, if applicable, the anticipated date of return to active employment. Ibis Employees shall be employees at will, subject to Abbott's employment policies and nothing herein shall be construed to limit Abbott's ability to (a) terminate or alter the employment terms of any Ibis Employee for any reason, including without cause, or (b) modify, amend or terminate any employee benefit plan, policy or arrangement.

(b) WARN. Isis covenants and agrees to cause Ibis to comply, if applicable, with all requirements specified under the Worker Adjustment and Retraining Notification Act of 1988 (the "WARN Act") or any similar or successor federal, state or local law, including the provision of appropriate notice to affected employees with respect to any "employment loss" (as defined in the WARN Act) that occurs on or prior to the Closing Date. Except as set forth on Schedule 8.11(b), no Ibis Employee has suffered an "employment loss" during the ninety (90)-day period prior to the date hereof. Isis shall update Schedule 8.11(b) as necessary to reflect all "employment losses" between the date hereof and prior to the Closing Date.

(c) COBRA. Isis shall retain responsibility for all liability for any health care continuation coverage or notice requirement under Section 4980B of the Code and Part G of Subtitle B of Title 1 of ERISA with respect to any Plan, including with respect to all former employees of Ibis or the Business, who are former employees thereof as of the Closing.

(d) Retirement Plans. Prior to or on the Closing Date, Isis and/or Ibis shall make all matching contributions and a pro-rated portion of any profit sharing contributions that would otherwise be made for the plan year (without regard to any year-end employment requirements) with respect to the Ibis Employees' contributions to any Plan that is intended to be qualified under Section 401(a) of the Code (the "Isis Retirement Plans"). Isis shall prior to the Closing: (A) amend each Isis Retirement Plan to cause the account balances or accrued benefits of Ibis Employees to be fully vested as of the Closing Date and (B) amend each Isis Retirement Plan that includes a cash or deferred arrangement under Section 401(k) of the Code to permit Ibis Employees with an outstanding plan loan to roll over such loan to Abbott's 401(k) plan. Abbott will cause its 401(k) plan to accept a direct rollover of the Ibis Employees' 401(k) account balance, including a direct rollover of any outstanding plan loan.

(e) Payroll Tax Reporting. Ibis, Isis and AMI agree that payroll reporting of the Ibis Employees will be treated in accordance with the Alternate Procedure set forth in Section 5 of Revenue Procedure 2004-53.

(f) Retention of Liability. Isis shall be solely responsible for, and retain all liabilities with respect to and Isis shall retain, bear and discharge all liabilities and obligations with respect to (i) all inactive Ibis Employees until such time as the inactive Ibis Employee returns to active employment with Ibis and (ii) all inactive Ibis Employees who fail to return to active employment with Ibis. Isis shall be solely responsible for, and retain all liabilities with respect to, all wages, salaries, commissions, bonuses, vacation pay and other compensation payable to any Ibis Employee for all periods through and including the Closing Date. AMI shall not assume liability for any retention, severance, change-of-control or similar agreements between Isis and any of the Ibis Employees, and Isis shall retain or assume liability for all obligations under any such retention, severance, change-of-control or similar agreements. For purposes of this Section 8.11, an "inactive Ibis Employee" shall mean any employee of Ibis who, as of the Closing Date, is on any type of leave of absence or who has been otherwise continuously absent from work with Ibis for any reason for longer than five (5) working days, other than for approved paid vacation.

(g) Full-Time Equivalents. From and after the date hereof, Isis and Ibis shall cause the number of full-time equivalent employees (not including temporary employees and consultants) of Ibis to be not greater than 70 in the aggregate and to be not less than 56 in the aggregate.

(h) No Third Party Rights. Nothing in this Agreement, express or implied, shall create a contract of employment with any Ibis Employee or a third party beneficiary relationship or otherwise amend or create any employee benefit plan of AMI or Ibis or confer any benefit, entitlement, or right upon any person or entity other than the parties hereto or result in AMI or Ibis having any liability under any Plan.

8.12 Consolidated Return. From and after the date hereof, Isis will file a consolidated Tax Return with respect to itself and Ibis in lieu of separate Tax Returns with respect to income Tax imposed by Chapter 1 of the Code for each Tax year beginning on or after January 1, 2008 through and including the Closing unless the provisions of the Code shall have been amended after the date hereof to disallow the filing of such consolidated Tax Returns. In

the event of an Internal Revenue Service audit of Isis arising out or related to the consolidation of Ibis and Isis in such consolidated Tax Return, Isis will promptly (but in any event within [***] notify AMI of such audit and allow AMI to participate and advise Ibis and Isis in connection with such audit.

8.13 Isis Intellectual Property License.

(a) To the extent Isis has not as of the Closing Date granted rights preventing Isis from making any further license grants, Isis hereby grants to Ibis a worldwide, fully-paid, royalty free, non-exclusive license (without the right to grant sublicenses, except to purchasers, distributors or resellers of Products to use, sell or resell, the amounts of Products purchased) under the Isis Licensed Intellectual Property to make, have made, import, use (in any field of use, including research performed internally and with collaborators, and in the sale of services), offer for sale, and sell Products. This license is transferable by Ibis to its Affiliates or to a successor in interest to Ibis without the prior written consent of Isis.

(b) Additionally, upon Ibis' request, Isis shall grant to Ibis worldwide, fully-paid, royalty free, non-exclusive licenses (without the right to grant sublicenses, except to purchasers, distributors or resellers of Products to use, sell or resell, the amounts of Products purchased) to any [***] make, have made, import, use (in any field of use, including research performed internally and with collaborators, and in the sale of services), offer for sale and sell Products, to the extent Isis has not previously granted rights preventing Isis from granting such licenses to Ibis. This right to license Isis' Intellectual Property is transferable by Ibis to its Affiliates or to a successor in interest to Ibis without the prior written consent of Isis.

(c) Until [***], Isis and its Affiliates shall not license any [***] for use with a [***]

8.14 [***].[***].

Following the Closing, Ibis shall pay to Isis all amounts in excess of $[***] that Ibis receives for the payment of [***], it being understood that the first $[***] of such amounts shall belong to Ibis; *provided*, that if the Closing does not occur on or before [***], then the first $[***] of such amounts shall not belong to Ibis, and Ibis will pay to Isis all amounts that Ibis receives for the payment of [***]. Following the Closing, Ibis shall collect such [***] using

commercially reasonably efforts, taking into account the manner in which Ibis collected similar receivables prior to the Closing Date. For Tax purposes, the Parties agree to treat all payments made under this Section 8.14 as adjustments to the Purchase Price, except to the extent any applicable Tax Law does not permit such treatment. If any Governmental Authority disputes treatment as an adjustment to the Purchase Price, the Party receiving notice of such dispute will promptly notify and consult the other Party concerning resolution of such dispute.

8.15 [***].

Following the Closing, Ibis shall be responsible for satisfying [***] claims from [***] related to the goods and services provided by Ibis prior to the Closing pursuant to the Contracts listed on Exhibit C, up to an amount not to exceed, with respect to each such Contract, the [***] listed on Exhibit C for such Contract (each a [***]).

8.16 Fees for Transition Services.

If the Closing occurs after [***], then AMI shall pay Isis, as additional consideration for the services provided pursuant to the Transition Services Agreement, an aggregate amount not to exceed (a) the absolute value of the difference between Ibis' [***], for the period beginning [***] and ending on the Closing Date, not to exceed $[***] per month, as calculated in accordance with GAAP, *minus* (b) $[***].

8.17 Updated Exhibits.

Within 10 Business Days following the Closing Date, Isis shall deliver to AMI Exhibit B prepared in the manner described in Section 1(w). In addition, by January 31, 2009, Isis shall deliver to AMI Exhibit C updated as of the Closing Date and prepared in the manner described in Section 1(gg). Both such Exhibits shall be attached thereafter to this Agreement.

Section 9. TERMINATION.

9.1 Termination. AMI or Isis may terminate this Agreement as follows:

(a) by mutual written consent at any time prior to the Closing;

(b) by giving written notice to the other at any time prior to Closing if there has been a material misrepresentation or breach on the part of the other Party of the representations, warranties or covenants set forth in this Agreement, which breach cannot be or has not been cured, in all material respects, within [***] after the giving of written notice of such breach to AMI or Isis, as applicable;

(c) if events have occurred which have made it impossible to satisfy a condition precedent to the terminating Party's obligations to consummate the transactions contemplated hereby unless such terminating Party's willful breach of this Agreement has caused the condition to be unsatisfied;

(d) by giving written notice to the other Party at any time prior to the Closing if the Closing shall not have occurred on or before the date that is [***] from the date hereof or, in the event that the applicable waiting periods (and any extensions thereof) under the HSR Act have not expired or otherwise been terminated (whether as a result of a "second request" or otherwise), the date that is [***] from the date hereof; *provided*, that neither AMI nor Isis shall be entitled to terminate this Agreement pursuant to this Section 9.1(d) if such Party's willful breach of this Agreement has prevented the consummation of the transactions contemplated hereby at or before such time.

9.2 Effect of Termination. In the event of termination of this Agreement by either AMI or Isis as provided in Section 9.1, this Agreement shall forthwith become null and void and there shall be no liability on the part of any Party to any other Party under this Agreement, except that the provisions of Section 1, this Section 9.2, Section 8.3, Section 8.4, Section 8.8, and Section 10 shall continue in full force and effect, except that nothing herein shall relieve any Party from liability for any breach of this Agreement prior to such termination.

Section 10. MISCELLANEOUS.

10.1 No Third Party Beneficiaries. Except as expressly provided in Section 8.2 with respect to members of the AMI Group and the Seller Group, this Agreement shall not confer any rights or remedies upon any Person other than the Parties and their respective successors and permitted assigns.

10.2 Entire Agreement. This Agreement, the Exhibits and Schedules hereto, the Transaction Documents and the other documents delivered pursuant hereto or referred to herein constitute the full and entire understanding and agreement between the Parties with regard to the subject hereof and no party will be liable for or bound to any other in any manner by any oral or written representations, warranties, covenants and agreements except as specifically set forth herein or therein. From and after the Closing, the Investment Documents shall terminate and be of no further force or effect except that such termination shall not relieve any Party from liability for any breach of such agreements prior to such termination.

10.3 Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. No Party may assign either this Agreement or any of its rights, interests or obligations hereunder without the prior written approval of the other Party; *provided* that AMI may (a) assign any or all of its rights and interests hereunder to one or more of its Affiliates, (b) designate one or more of its Affiliates to perform its obligations hereunder (in any or all of which cases AMI nonetheless shall remain responsible for the performance of all of its obligations hereunder), and (c) assign any or all of its rights and interests hereunder in connection with a Change of Control of AMI.

10.4 Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together will constitute one and the same instrument. This Agreement and any signed agreement or instrument entered into in connection with this

Agreement, and any amendments hereto or thereto, to the extent signed and delivered by means of a facsimile machine or other electronic means, shall be treated in all manner and respects as an original agreement or instrument and shall be considered to have the same binding legal effect as if it were the original signed version thereof delivered in person. At the request of any party hereto or to any such agreement or instrument, each other party hereto or thereto shall re-execute original forms thereof and deliver them to all other parties. No party hereto or to any such agreement or instrument shall raise the use of a facsimile machine or other electronic means to deliver a signature or the fact that any signature or agreement or instrument was transmitted or communicated through the use of a facsimile machine or other electronic means as a defense to the formation of a contract and each such party forever waives any such defense.

10.5 Headings. The section headings contained in this Agreement are inserted for convenience only and shall not affect in any way the meaning or interpretation of this Agreement.

10.6 Notices. All notices, requests, demands, claims, and other communications hereunder will be in writing. Any notice, request, demand, claim, or other communication hereunder shall be deemed duly given (a) when delivered on a Business Day, if

personally delivered or sent by facsimile or other electronic means (subject to confirmation of such delivery), on such Business Day, (b) when delivered other than on a Business Day, if personally delivered or sent by facsimile or other electronic means (subject to confirmation of such delivery), on the first Business Day after dispatch, (c) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (d) on the third Business Day following the date of mailing, if sent by mail, in each case, addressed to the intended recipient as set forth below:

If to Ibis, to:

Ibis Biosciences Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: President
Facsimile: (760) 603-4653

If to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Financial Officer
Facsimile: (760) 603-4650

with a copy to:

1896 Rutherford Road
Carlsbad, CA 92008
Attention: General Counsel
Facsimile: (760) 268-4922

If to AMI:

Abbott Molecular Inc.
c/o Abbott Laboratories
Corporate Transactions and Medical Products Legal Operations
Dept. 322, Bldg. AP6A
100 Abbott Park Road
Abbott Park, IL 60064-6010
Attention: Vice President and Associate General Counsel
Facsimile: (847) 938-1206

with a copy to:

Kirkland & Ellis LLP
200 East Randolph Drive
Chicago, IL 60601
Attn: R. Scott Falk, P.C.
R. Henry Kleeman
Facsimile: (312) 861-2200

Any Party may send any notice, request, demand, claim or other communication hereunder to the intended recipient at the address set forth above using any other means, but no such notice, request, demand, claim or other communication shall be deemed to have been duly given unless and until it actually is received by the intended recipient. Any Party may change the address to which notices, requests, demands, claims and other communications hereunder are to be delivered by giving the other Party notice in the manner herein set forth.

10.7 Governing Law. This Agreement shall be governed by and construed in accordance with the domestic laws of the State of Delaware without giving effect to any choice or conflict of law provision or rule (whether of the State of Delaware or any other jurisdiction) that would cause the application of the laws of any jurisdiction other than the State of Delaware.

10.8 Alternative Dispute Resolution Procedure. The Parties recognize that from time to time a dispute may arise relating to a Party's rights or obligations under this Agreement or the other Transaction Documents. The Parties agree that any such dispute shall be resolved by the Alternative Dispute Resolution ("ADR") provisions set forth in Exhibit H the result of which shall be binding upon the Parties.

10.9 Amendments and Waivers. No amendment of any provision of this Agreement shall be valid unless the same shall be in writing and signed by AMI and Isis. No waiver by any Party of any default, misrepresentation, or breach of warranty or covenant hereunder, whether intentional or not, shall be deemed to extend to any prior or subsequent default, misrepresentation or breach of warranty or covenant hereunder or affect in any way any rights arising by virtue of any prior or subsequent such occurrence.

10.10 Delays or Omissions. It is agreed that no delay or omission to exercise any right, power or remedy accruing to any Party, upon any breach, default or noncompliance by another party under a Transaction Document or otherwise, will impair any such right, power or remedy, nor will it be construed to be a waiver of any such breach, default or noncompliance, or any acquiescence therein, or of or in any similar breach, default or noncompliance thereafter occurring. It is further agreed that any waiver, permit, consent or approval of any kind or character on any Party's part of any breach, default or noncompliance under a Transaction Document or otherwise or any waiver on such Party's part of any provisions or conditions of a Transaction Document, or otherwise must be in writing and will be effective only to the extent specifically set forth in such writing. All remedies, either under a Transaction Document, Ibis' Certificate of Incorporation, bylaw, or otherwise afforded to any party, will be cumulative and not alternative.

10.11 Incorporation of Exhibits and Schedules. The exhibits and Schedules identified in this Agreement are incorporated herein by reference and made a part hereof. The Parties acknowledge and agree that (a) the Disclosure Schedules are arranged in sections corresponding to the sections and paragraphs of this Agreement and the disclosures therein qualify the specifically referenced corresponding representations and warranties of the Parties

contained in this Agreement, (b) to the extent this Agreement requires disclosure of any matter, such matter disclosed pursuant to one provision, subprovision, section or subsection of the Disclosure Schedules shall be deemed disclosed only to the extent actually disclosed with respect to the specific provision, subprovision, section or subsection of the Disclosure Schedule that it is actually disclosed pursuant to and (c) section numbers and titles inserted in the Disclosure Schedules are for convenience of reference only and shall to no extent have the effect of amending or changing the express description of such sections of the Disclosure Schedules as set forth in this Agreement. Information set forth in each section of the Disclosure Schedules specifically refers to the section of this Agreement to which such information is responsive, and such information shall not be deemed to have been disclosed with respect to any statement made in any other section of this Agreement. Any capitalized terms used in any Schedule but not otherwise defined therein shall have the meanings ascribed to such terms in this Agreement.

10.12 Construction. The Parties acknowledge and agree that they have been represented by counsel during the negotiation, preparation and execution of this Agreement and, therefore, waive the application of any Law or rule of construction providing that ambiguities in an agreement or other document shall be construed against the Party drafting such agreement or document. Where specific language is used to clarify by example a general statement contained herein, such specific language shall not be deemed to modify, limit or restrict in any manner the construction of the general statement to which it relates. When the context so requires the word "or" when used herein shall mean "and/or." All pronouns contained herein, and any variations thereof, will be deemed to refer to the masculine, feminine or neutral, singular or plural, as the identity of the Parties hereto may require. Other than with respect to Section 3.2, Section 4.1 and the preamble to Section 5.1, the words, "provided to," "delivered" or "made available" or words of similar import when used in this Agreement to refer to obligations of Isis and/or Ibis to "provide," "deliver" or "make available" materials to AMI mean "made available in the online dataroom maintained by Isis at [***] at least three (3) Business Days prior to the date hereof". Unless otherwise provided therein, when used in any Transaction Document or Schedule, "Dollars" or "$" means the lawful currency of the United States of America.

10.13 Remedies. Each of the Parties acknowledges and agrees that the other Party would be damaged irreparably in the event any of the provisions of this Agreement are not performed in accordance with their specific terms or otherwise are breached. Accordingly, each of the Parties agrees that, subject to Section 10.8 the other Party shall be entitled to an injunction or injunctions to prevent breaches of the provisions of this Agreement and to enforce specifically this Agreement and the terms and provisions hereof in any action instituted in any court of the United States or any state thereof having jurisdiction over the Parties and the matter (subject to Section 10.8 above), in addition to any other remedy to which they may be entitled, at law or in equity.

10.14 Severability. In the event that any provision of this Agreement, or the application thereof, becomes or is declared by a court of competent jurisdiction to be illegal, void or unenforceable, the remainder of this Agreement shall continue in full force and effect and the application of such provision to other Persons or circumstances shall be interpreted so as reasonably to effect the intent of the Parties hereto. The Parties further agree to replace such void or unenforceable provision of this Agreement with a valid and enforceable provision that

will achieve, to the extent possible, the economic, business and other purposes of such void or unenforceable provision.

10.15 No Other Compensation.

The Parties hereby agree that the terms of the Transaction Documents fully define all consideration, compensation and benefits, monetary or otherwise, to be paid, granted or delivered by Isis or Ibis to AMI or Abbott and by AMI or Abbott to Isis or Ibis in connection with the transactions contemplated herein and therein. No Party previously has paid or entered into any other commitment to pay, whether orally or in writing, any employee of any other Party, directly or indirectly, any consideration, compensation or benefits, monetary or otherwise, in connection with the transactions contemplated in the Transaction Documents.

* * * * *

[Remainder of page intentionally left blank; Signatures on following page]

IN WITNESS WHEREOF, the Parties hereto have executed this Stock Purchase Agreement as of the date first above written.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer and Chief Financial Officer

IBIS BIOSCIENCES, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: CFO

ABBOTT MOLECULAR INC.

By: */s/ Stafford O'Kelly*

Name: Stafford O'Kelly

Title: President

SIGNATURE PAGE TO STOCK PURCHASE AGREEMENT

LIST OF EXHIBITS

EXHIBIT A

[***]

[Attached]

[***]

EXHIBIT B

COMMERCIAL REVENUE DETAIL

[Attached]

[***]

EXHIBIT C

[***]

[Attached]

[***]

EXHIBIT D

ISIS LICENSED INTELLECTUAL PROPERTY

[Attached]

[***]

EXHIBIT E

TRANSITION SERVICES AGREEMENT

[Attached]

EXHIBIT E

TRANSITION SERVICES AGREEMENT

THIS TRANSITION SERVICES AGREEMENT is made and entered into as of this [ ] day of **[ ]**, 2009, by and between Ibis Biosciences, Inc., a Delaware corporation ("Ibis"), and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis"). Ibis and Isis are sometimes referred to herein individually as a "Party" and collectively as the "Parties."

WHEREAS, Ibis, Isis and Abbott Molecular Inc., a Delaware corporation ("AMI"), have entered into a Stock Purchase Agreement, dated as of December 17, 2008 (the "Acquisition Agreement");

WHEREAS, pursuant to the Acquisition Agreement, among other things, AMI has acquired the Remaining Shares of Capital Stock of Ibis such that, as of the date hereof, Ibis is a wholly-owned subsidiary of AMI;

WHEREAS, to facilitate an orderly transition of the Business, Isis has agreed to provide certain transition services to Ibis, as set forth herein; and

WHEREAS, Ibis has agreed to cooperate with and offer support to Isis in connection with closing the books of Ibis as they relate to the operation of the Business prior to the Closing, as set forth herein.

NOW, THEREFORE, in consideration of the mutual promises, representations, warranties, and covenants hereinafter set forth and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

Section 1. Definitions.

Capitalized terms used and not defined herein shall have the meanings ascribed to such terms in the Acquisition Agreement. In addition to the terms defined elsewhere herein and in the Acquisition Agreement, the following terms when used in this Agreement shall have the following meanings:

"Acquisition Agreement" has the meaning set forth in the Recitals.

"AMI" has the meaning set forth in the Recitals.

"Additional Services" has the meaning set forth in Section 2(b).

"Agreement" means this Transition Services Agreement, including all Schedules and Exhibits attached hereto, as it may be amended from time to time pursuant to the provisions hereof.

"Fees" has the meaning set forth in Section 2(f).

"Ibis" has the meaning set forth in the Preamble.

"Initial Services" has the meaning set forth in Section 2(a).

"Isis" has the meaning set forth in the Preamble.

"Schedule of Services" has the meaning set forth in Section 2(a).

"Services" has the meaning set forth in Section 2(b).

"Term" has the meaning set forth in Section 4(a).

"Third Party" means any Person other than Isis, Ibis and any of their respective Affiliates.

Section 2. Services.

(a) Initial Services. Commencing on the Closing Date, Isis shall provide to Ibis the applicable services (the "Initial Services") set forth on the Schedule of Services attached hereto as Exhibit A (the "Schedule of Services").

(b) Additional Services. At any time during the Term, Ibis may request in writing that Isis provide other services to Ibis hereunder. If Isis consents in writing to such request, which consent shall not be unreasonably withheld if such requested service has been provided by Isis to the Business during the 12-month period ending on the Closing Date, then the Schedule of Services shall be amended to add such services (the "Additional Services" and, together with the Initial Services, the "Services"). Each Schedule describing an Additional Service shall set forth a description of such Additional Service, the time period during which such Additional Service will be provided, the charges for such Additional Service and any other terms applicable thereto.

(c) Audit Assistance. Each of the Parties and their respective Affiliates are or may be subject to regulation and audit by Governmental Authorities, standards organizations, customers or other Parties to contracts with such Parties under Applicable Law and contract provisions. If a Governmental Authority, standards organization, or customer or other party to a contract with a Party or an Affiliate of a Party exercises its right to examine or audit such Party's or its Affiliate's books, records, documents or accounting practices and procedures pursuant to such Applicable Law, standards or contract provisions and such audit or examination relates to the Services or the conduct of the Business prior to the Closing, the other Party shall provide (at its own expense), all reasonable assistance requested by the Party that is subject to the audit in responding to such audits or requests for information, to the extent that such assistance or information is within the reasonable control of the cooperating Party and is related to the Services or the conduct of the Business prior to the Closing. Specifically, Ibis' accounting group and contract administration group will assist Isis in all activities related to Ibis' work performed under its government contracts prior to the Closing. These activities include (i) preparing and sending invoices related to 2008 activity, (ii) preparing and filing on or prior to June 30, 2009 the 2008 incurred cost submission, (iii) planning, preparing for and executing the 2008 project-specific audit (A-133 audit) so that the audit report is filed on or prior to September 30, 2009, (iv) contract closeout audits, (v) incurred cost submission audits and (vi) any other contract audits pertaining to work Ibis performed prior to the Closing. Additionally, Ibis' accounting

group and contract administration group will make available to Isis any documentation related to government contracts, government billings, indirect rate calculations or any other documents related to government contracts under which Ibis performed work prior to the Closing that Isis reasonably requests in writing. Ibis shall perform such services using due care and in a commercially reasonable manner that is substantially similar in nature, quality and timeliness to the same tasks performed by Ibis prior to the Closing Date. All information provided pursuant to this Section 2(c) shall be subject to Section 8.8 of the Acquisition Agreement (Confidentiality).

(d) Accounting and IT Services. For [***] to Isis, Ibis will provide Isis with the accounting and information technology services set forth in Exhibit B until the termination date set forth in Exhibit B for each such service.

(e) Access. Subject to Section 8.8 of the Acquisition Agreement (Confidentiality), Ibis shall make available on a timely basis to Isis all information and materials reasonably requested by Isis that are necessary to enable Isis to provide the relevant Services.

(f) Performance of Services. Except as specifically set forth in the applicable Schedule of Services, Isis shall perform all Services using due care and in a commercially reasonable manner that is substantially similar in nature, quality and timeliness to analogous services provided to Ibis prior to the Closing Date.

(g) Charges for Services. Subject to adjustment in accordance with Section 8.16 of the Acquisition Agreement (Fees for Transition Services), the aggregate charges for all Initial Services shall be [***] (the "Fees"), which shall be payable in equal monthly installments. The charges for an Additional Service, if any, shall be described in detail on the Schedule of Services with respect to such Additional Service. Ibis will pay the applicable charges for the Services in accordance with Section 3 (Billing; Taxes).

(h) Transitional Nature of Services. The Parties acknowledge the transitional nature of the Services and agree to cooperate in good faith and to use reasonable best efforts to effectuate a smooth transition of the Services from Isis to Ibis (or its Affiliates).

(i) Cooperation. In the event that (i) there is nonperformance of any Service as a result of an event described in Section 7(c) (Force Majeure), or (ii) the provision of a Service would violate Applicable Law, the Parties agree to work together in good faith to arrange for an alternative means by which Ibis may obtain, at Ibis' sole cost, the Services so affected.

(j) Use of Third Parties to Provide Services. Isis may perform its obligations through its Affiliates or, if prior to the Closing, Isis obtains analogous services for itself from agents, subcontractors or independent contractors, Isis may perform its obligations hereunder through the use of agents, subcontractors or independent contractors. If, prior to the Closing, Isis is not obtaining analogous services for itself from agents, subcontractors or independent contractors, Isis may perform its obligations hereunder through the use of agents, subcontractors or independent contractors only upon obtaining the prior written consent of Ibis, which consent shall not be unreasonably withheld or delayed. Notwithstanding the foregoing, Isis shall not be relieved of its obligations under this Agreement by use of such Affiliates, agents, subcontractors or contractors.

Section 3. Billing; Taxes.

(a) Procedure. For the Initial Services, Isis shall invoice Ibis monthly for the prior month's pro rata share of the Fees. Unless otherwise mutually agreed by the Parties in writing, for Additional Services, if any, Isis shall invoice Ibis on a quarterly basis for the Additional Services. Ibis shall pay invoiced amounts within 45 days of receipt of the invoice.

(b) Taxes. Ibis shall pay any and all Taxes incurred in connection with Isis' provision of the Services, including all withholding Taxes required by Applicable Law and all sales, use, value-added, and similar Taxes, but excluding Taxes based on Isis' net income.

Section 4. Term and Termination.

(a) Term. The term of this Agreement (the "Term") shall commence on the Closing Date and, unless terminated earlier pursuant to Section 4(b), shall terminate at the close of business on [***]

(b) Early Termination. This Agreement shall automatically terminate upon the earlier of (i) termination of the performance of the last Service or (ii) the date Ibis is no longer occupying Isis' premises. If Ibis intends to vacate Isis' premises before [***], then Ibis will provide Isis at least 30 days advance written notice.

Section 5. Software License. Isis hereby grants to Ibis a worldwide, fully paid, royalty free, perpetual, nonexclusive license (without the right to grant sublicenses, except to Affiliates of Ibis) to all of Isis' rights in (a) the software programs entitled [***], and [***] (and any dependent programs specifically referenced therein) used in support of the Ibis manufacturing process to facilitate [***], and (b) the software application Ibis uses to enter employee time. Such software is hereby licensed to Ibis as-is. Each party acknowledges and agrees that Isis has provided the source code for the software described above to Ibis.

Section 6. Indemnification.

(a) Isis shall indemnify, defend and hold harmless AMI, Ibis and their respective officers, directors, shareholders, employees, representatives, agents and Affiliates (the "Ibis Indemnified Parties") from and against all Losses actually suffered or incurred by them to the extent arising out of or resulting from (i) a breach of this Agreement by Isis or any of its Affiliates or (ii) the handling, storage, disposal or transport of any Hazardous Materials by Isis or any of its Representatives, except, in each case, to the extent such Losses arise out of the negligence, willful misconduct or bad faith of any Ibis Indemnified Party.

(b) Ibis shall indemnify, defend and hold harmless Isis and its officers, directors, shareholders, employees, representatives, agents and Affiliates (the "Isis Indemnified Parties") from and against all Losses actually suffered or incurred by them to the extent arising out of or resulting from (i) a breach of this Agreement by Ibis or any of its Affiliates, (ii) the handling, storage, disposal or transport of any Hazardous Materials by Ibis or any of its Representatives, or (iii) the occupancy of Isis' premises by Ibis or any of its Representatives (including any Third Party invited onto Isis' premises by Ibis), except, in each case, to the extent

such Losses arise out of the negligence, willful misconduct or bad faith of any Isis Indemnified Party.

(c) If any Third Party shall notify any Party to this Agreement (the "Indemnified Party") with respect to any matter which may give rise to a claim (a "Third Party Claim") for indemnification against any other Party to this Agreement (the "Indemnifying Party") under this Section 6, then the Indemnified Party shall notify the Indemnifying Party thereof; provided that the failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party of its obligations hereunder except to the extent such failure shall have actually materially prejudiced the Indemnifying Party. Once the Indemnified Party has given notice of the matter to the Indemnifying Party, the Indemnified Party shall defend against the matter in any manner it reasonably may deem appropriate. The Indemnifying Party may, at its sole cost and expense, participate in the defense of such Claim with co-counsel of its choice. The Indemnified Party will not consent to the entry of any judgment with respect to the matter or enter into any settlement with respect to the matter without the Indemnifying Party's prior written consent (not to be unreasonably withheld, conditioned or delayed). Notwithstanding anything herein to the contrary, the Indemnifying Party shall not have the right to participate in such defense if the claim in which the Indemnifying Party seeks to participate (i) seeks non-monetary, including injunctive, relief, (ii) involves criminal allegations against an Indemnified Party or (iii) is one in which the Indemnifying Party is also a party and joint representation would be inappropriate or there may be legal defenses available to the Indemnified Party which are different from or additional to those available to the Indemnifying Party.

(d) No Ibis Indemnified Party or Isis Indemnified Party shall be entitled to recover any Losses relating to any matter arising under any provision of this Agreement to the extent that any such Person has already recovered Losses with respect to such matter pursuant to the Acquisition Agreement.

Section 7. Miscellaneous.

(a) Limitations On Liability. EXCEPT TO THE EXTENT THAT ANY PUNITIVE, INCIDENTAL, CONSEQUENTIAL, SPECIAL OR INDIRECT DAMAGES ARE AWARDED IN CONNECTION WITH A THIRD PARTY CLAIM AGAINST AN INDEMNIFIED PARTY AND SUCH INDEMNIFIED PARTY IS ENTITLED TO BE INDEMNIFIED HEREUNDER AS A RESULT OF THE FACTS OR CIRCUMSTANCES GIVING RISE TO SUCH THIRD PARTY CLAIM, IN NO EVENT SHALL ANY PARTY, ITS OFFICERS, DIRECTORS, SHAREHOLDERS, EMPLOYEES, REPRESENTATIVES, AGENTS OR AFFILIATES BE LIABLE TO ANOTHER PARTY FOR ANY PUNITIVE, INCIDENTAL, CONSEQUENTIAL, SPECIAL OR INDIRECT DAMAGES IN CONNECTION WITH THE PERFORMANCE OF THIS AGREEMENT, EVEN IF THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES, AND EACH PARTY HEREBY WAIVES ON BEHALF OF ITSELF AND THE IBIS INDEMNIFIED PARTIES OR THE ISIS INDEMNIFIED PARTIES, AS THE CASE MAY BE, ANY CLAIM FOR SUCH DAMAGES, INCLUDING ANY CLAIM FOR PROPERTY DAMAGE OR LOST PROFITS, WHETHER ARISING IN CONTRACT, TORT OR OTHERWISE.

(b) Title To Intellectual Property. Except as explicitly provided in Section 5 (Software License) Ibis acknowledges that it shall acquire no right, title or interest (including any

license rights or rights of use) in any intellectual property that is owned or licensed by Isis, by reason of the provision of the Services provided hereunder. Ibis shall not remove or alter any copyright, trademark, confidentiality or other proprietary notices that appear on any intellectual property owned or licensed by Isis, and Ibis shall reproduce any such notices on any and all copies thereof. Ibis shall not attempt to decompile, translate, reverse engineer or make excessive copies of any intellectual property owned or licensed by Isis, and Ibis shall promptly notify Isis of any such attempt, regardless of whether by Ibis or any Third Party, of which Ibis becomes aware. Nothing in this Agreement shall affect any rights granted to a Party under the Acquisition Agreement.

(c) Force Majeure. No Party shall be liable to another Party if, and to the extent that, the performance or delay in performance of any of its obligations under this Agreement is prevented, restricted, delayed or interfered with due to circumstances beyond the reasonable control of such Party, including, but not limited to, government legislation, fires, floods, explosions, epidemics, accidents, acts of God, wars, acts of terrorism, riots, strikes, lockouts or other concerted acts of workers and/or acts of government. The Party claiming an event of force majeure shall promptly notify the other Party in writing, and provide full particulars of the cause or event and the date of first occurrence thereof, as soon as possible after the event and also keep the other Party informed of any further developments. The Party so affected shall use its reasonable best efforts to remove the cause of non-performance, and both the Parties shall resume performance hereunder with the utmost dispatch when such cause is removed unless this Agreement has previously been terminated under Section 4 (Term and Termination).

(d) Independent Contractors. The Parties each acknowledge that they are separate entities, each of which has entered into this Agreement for independent business reasons. The relationships of the Parties hereunder are those of independent contractors and nothing contained herein shall be deemed to create a joint venture, partnership or any other relationship.

(e) Survival. Section 1 (Definitions), Section 2(c) (Audit Assistance), Section 3 (Billing; Taxes), Section 5 (Software License), Section 6 (Indemnification) and Section 7 (Miscellaneous), shall survive any expiration or termination of this Agreement.

(f) No Third Party Beneficiaries. Except as expressly contemplated in Section 6 with respect to Ibis Indemnified Parties and Ibis Indemnified Parties, this Agreement shall not confer any rights or remedies upon any Person other than the Parties and their respective successors and permitted assigns.

(g) Entire Agreement. This Agreement constitutes the full and entire understanding and agreement between the Parties with regard to the subject hereof and no party will be liable for or bound to any other in any manner by any oral or written representations, warranties, covenants and agreements except as specifically set forth herein or therein.

(h) Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. No Party may assign either this Agreement or any of its rights, interests or obligations hereunder without the prior written approval of the other Party; *provided* that Ibis may (i) assign any or all of its rights

and interests hereunder to one or more of its Affiliates, (ii) designate one or more of its Affiliates to perform its obligations hereunder (in any or all of which cases Ibis nonetheless shall remain responsible for the performance of all of its obligations hereunder), and (c) assign any or all of its rights and interests hereunder in connection with a Change of Control of Ibis or AMI.

(i) Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which together will constitute one and the same instrument. This Agreement and any signed agreement or instrument entered into in connection with this Agreement, and any amendments hereto or thereto, to the extent signed and delivered by means of a facsimile machine or other electronic means, shall be treated in all manner and respects as an original agreement or instrument and shall be considered to have the same binding legal effect as if it were the original signed version thereof delivered in person. At the request of any party hereto or to any such agreement or instrument, each other party hereto or thereto shall re-execute original forms thereof and deliver them to all other parties. No party hereto or to any such agreement or instrument shall raise the use of a facsimile machine or other electronic means to deliver a signature or the fact that any signature or agreement or instrument was transmitted or communicated through the use of a facsimile machine or other electronic means as a defense to the formation of a contract and each such party forever waives any such defense.

(j) Headings. The section headings contained in this Agreement are inserted for convenience only and shall not affect in any way the meaning or interpretation of this Agreement.

(k) Notices. All notices, requests, demands, claims, and other communications hereunder will be in writing. Any notice, request, demand, claim, or other communication hereunder shall be deemed duly given (i) when delivered on a Business Day, if personally delivered or sent by facsimile or other electronic means (subject to confirmation of such delivery), on such Business Day, (ii) when delivered other than on a Business Day, if personally delivered or sent by facsimile or other electronic means (subject to confirmation of such delivery), on the first Business Day after dispatch, (iii) on

the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (iv) on the third Business Day following the date of mailing, if sent by mail, in each case, addressed to the intended recipient as set forth below:

If to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Financial Officer
Facsimile: (760) 603-4650

with a copy to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: General Counsel
Facsimile: (760) 268-4922

If to Ibis, to:

Ibis Biosciences Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: General Manager
Facsimile: (760) 603-4653

with copies to:

Abbott Molecular Inc.
c/o Abbott Laboratories
Corporate Transactions and Medical Products Legal Operations
Dept. 322, Bldg. AP6A
100 Abbott Park Road
Abbott Park, Illinois 60064-6010
Attention: Vice President and Associate General Counsel
Facsimile: (847) 938-1206

and:

Kirkland & Ellis LLP
200 East Randolph Drive
Chicago, Illinois 60601
Attn: R. Scott Falk, P.C.
R. Henry Kleeman
Facsimile: (312) 861-2200

Any Party may send any notice, request, demand, claim or other communication hereunder to the intended recipient at the address set forth above using any other means, but no such notice, request, demand, claim or other communication shall be deemed to have been duly given unless and until it actually is received by the intended recipient. Any Party may change the address to which notices, requests, demands, claims and other communications hereunder are to be delivered by giving the other Party notice in the manner herein set forth.

(l) Governing Law. This Agreement shall be governed by and construed in accordance with the domestic laws of the State of Delaware without giving effect to any choice or conflict of law provision or rule (whether of the State of Delaware or any other jurisdiction) that would cause the application of the laws of any jurisdiction other than the State of Delaware.

(m) Alternative Dispute Resolution Procedure. The Parties recognize that from time to time a dispute may arise relating to either Party's rights or obligations under this Agreement. The Parties agree that any such dispute shall be resolved by the Alternative Dispute

Resolution ("ADR") provisions set forth in Exhibit E of the Acquisition Agreement, the result of which shall be binding upon the Parties.

(n) Amendments and Waivers. No amendment of any provision of this Agreement shall be valid unless the same shall be in writing and signed by Ibis and Isis. No waiver by any Party of any default, misrepresentation, or breach of warranty or covenant hereunder, whether intentional or not, shall be deemed to extend to any prior or subsequent default, misrepresentation or breach of warranty or covenant hereunder or affect in any way any rights arising by virtue of any prior or subsequent such occurrence.

(o) Construction. The Parties acknowledge and agree that they have been represented by counsel during the negotiation, preparation and execution of this Agreement and, therefore, waive the application of any Law or rule of construction providing that ambiguities in an agreement or other

document shall be construed against the Party drafting such agreement or document. Where specific language is used to clarify by example a general statement contained herein, such specific language shall not be deemed to modify, limit or restrict in any manner the construction of the general statement to which it relates. When the context so requires the word "or" when used herein shall mean "and/or." All pronouns contained herein, and any variations thereof, will be deemed to refer to the masculine, feminine or neutral, singular or plural, as the identity of the Parties hereto may require. Unless otherwise provided therein, when used in any Transaction Document or Schedule, "Dollars" or "$" means the lawful currency of the United States of America.

(p) Remedies. Each of the Parties acknowledges and agrees that the other Party would be damaged irreparably in the event any of the provisions of this Agreement are not performed in accordance with their specific terms or otherwise are breached. Accordingly, each of the Parties agrees that, subject to Section 7(m), the other Party shall be entitled to an injunction or injunctions to prevent breaches of the provisions of this Agreement and to enforce specifically this Agreement and the terms and provisions hereof in any action instituted in any court of the United States or any state thereof having jurisdiction over the Parties and the matter (subject to Section 7(m), above), in addition to any other remedy to which they may be entitled, at law or in equity.

(q) Severability. In the event that any provision of this Agreement, or the application thereof, becomes or is declared by a court of competent jurisdiction to be illegal, void or unenforceable, the remainder of this Agreement shall continue in full force and effect and the application of such provision to other Persons or circumstances shall be interpreted so as reasonably to effect the intent of the Parties hereto. The Parties further agree to replace such void or unenforceable provision of this Agreement with a valid and enforceable provision that will achieve, to the extent possible, the economic, business and other purposes of such void or unenforceable provision.

[Remainder of page intentionally left blank; Signatures on following page]

IN WITNESS WHEREOF, the Parties have executed this Transition Services Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

By: _____
Name:
Title:

IBIS BIOSCIENCES, INC.

By: _____
Name:
Title:

SIGNATURE PAGE TO TRANSITION SERVICES AGREEMENT

EXHIBIT A

SCHEDULE OF SERVICES

EXHIBIT B

ACCOUNTING AND IT SERVICES

EXHIBIT E-1

LIST OF TRANSITION SERVICES

Health, Safety and Environment

· services to be defined in the areas of: hazardous waste, biological waste, training, regulatory and permitting and general safety

Shipping and Receiving

· packaging, receiving, shipping and receipt distribution processing (exclusive of packaging material cost, fedex charges and postage costs, which shall be AMI's responsibility)

Office and Facilities

· janitorial, break room services, copiers, fax, telephone system (exclusive of long distance charges, which shall be AMI's responsibility) and laboratory services

· facility support as provided immediately prior to the Closing Date (exclusive of materials and labor related to new construction projects, if any)

Occupancy

· office and laboratory furniture
· utilities
· reception
· security

IT

· limited consulting services required to ensure the Business is functional immediately after the Closing.

EXHIBIT F

[***]

EXHIBIT G

PRESS RELEASE

[Attached]

Abbott Exercises Its Option to Acquire Ibis Biosciences, a Subsidiary of Isis

CARLSBAD, Calif. and ABBOTT PARK, Ill., Dec 17, 2008 /PRNewswire-FirstCall via COMTEX News Network/—

Total acquisition price will be $215 million

Acquisition will expand Abbott's position in molecular diagnostics for infectious disease

Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Abbott (NYSE: ABT) announced today that Abbott has exercised its option to purchase the remaining equity ownership in Ibis Biosciences, Inc., an Isis subsidiary, for a closing purchase price of $175 million. In addition to the closing purchase price, Isis will receive earn out payments from Abbott tied to post-closing sales of Ibis systems, including instruments and assay kits.

Earlier this year, Abbott invested $40 million in Ibis in exchange for approximately 18.6% of Ibis' outstanding equity. This investment, along with the $175 million that would be due at closing, would result in a total acquisition price of $215 million plus earn out payments.

The closing of the acquisition of the remaining equity ownership in Ibis is subject to the satisfaction of the terms and conditions of a stock purchase agreement that has been executed by the parties, including obtaining clearance under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, and is expected to occur in January, 2009.

"Abbott's confidence in Ibis is reflected in its decision to invest in Ibis' technology and to exercise its option to purchase Ibis. We have already presented development plans for the next-generation instrument that will facilitate our rapid growth into clinical diagnostics," said Michael Treble, President of Ibis. "This year we have made substantial progress by advancing our broad pathogen detection and characterization capabilities and establishing a foundation for our commercial clinical diagnostic products. We look forward to continuing this progress."

"The broad applicability of Ibis' technology has been demonstrated in biodefense applications, microbial forensics and infectious disease detection and surveillance, and we believe that it has the potential to be a powerful tool in the detection and surveillance of infectious diseases in the hospital and clinical settings," added Stafford O'Kelly, Vice President, Molecular Diagnostics, Abbott.

"Ibis is an example of Isis' broad innovation, and will provide substantial benefit to our shareholders, both now as well as in the future, as Isis receives earn out payments associated with sales of Ibis products," said Stanley Crooke, M.D., Ph.D., Chairman and CEO of Isis. "Ibis has refined its approach toward larger commercial markets, and we believe its relationship with Abbott will allow Ibis to continue to move quickly forward along this path."

About Ibis T5000 Biosensor System and Ibis Biosciences, Inc.

Ibis Biosciences, Inc., a majority-owned subsidiary of Isis Pharmaceuticals, has developed and is commercializing the Ibis T5000(TM) Biosensor System for rapid identification and characterization of infectious agents. The Ibis T5000 is currently intended for research use only and not for use in diagnostic procedures. It is capable of identifying virtually all bacteria, viruses

and fungi, and can provide information about drug resistance, virulence and strain type of these pathogens. Commercial applications for the Ibis T5000 Biosensor System include epidemiologic surveillance, monitoring of pandemic diseases, identification of emerging or previously unknown pathogens, forensic characterization of human samples, identification of sources of hospital-associated infections, and, in the future, human infectious disease diagnostics. Ibis develops, manufactures and markets Ibis T5000 instruments and assay kits. Additional information about Ibis can be found by selecting the Ibis link from Isis' homepage at www.isispharm.com.

About Abbott Molecular

Abbott's molecular diagnostics business, headquartered in Des Plaines, Ill., provides physicians with critical information based on the early detection of pathogens and key changes in patients' genes and chromosomes, allowing for earlier diagnosis, selection of appropriate therapies and monitoring of disease progression. The business includes instruments and reagents used to conduct sophisticated analysis of patient DNA and RNA.

About Abbott

Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics. The company employs more than 68,000 people and markets its products in more than 130 countries.

Abbott's news releases and other information are available on the company's Web site at www.abbott.com.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as its Ibis Biosciences subsidiary and the commercial potential of Ibis' technologies and products in development. Any statement describing Isis' 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. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove

correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2007, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

Private Securities Litigation Reform Act of 1995 —A Caution Concerning Forward-Looking Statements

Some statements in this news release may be forward-looking statements for the purposes of the Private Securities Litigation Reform Act of 1995. Abbott cautions that these forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated. Economic, competitive, governmental, technological and other factors that may affect Abbott's operations are discussed in Item 1A, "Risk Factors," to Abbott's Annual Report on Securities and Exchange Commission Form 10-K for the year ended December 31, 2007, and in Item 1A, "Risk Factors," to Abbott's Quarterly Reports on Securities and Exchange Commission Form 10-Q for the quarters ended June 30, 2008, and September 30, 2008, and are incorporated by reference. Abbott undertakes no obligation to release publicly any revisions to forward-looking statements as a result of subsequent events or developments.

In this press release, unless the context requires otherwise, "Isis" and "Company" refers to Isis Pharmaceuticals and its subsidiaries and joint venture.

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Ibis Biosciences and Ibis T5000 are trademarks of Ibis Biosciences, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics LLC.

EXHIBIT H

ADR PROCEDURE

To begin the ADR process, a Party first must send written notice of the dispute to the other Party for attempted resolution by good faith negotiations between their respective presidents (or their designees) of the affected subsidiaries, divisions, or business units within twenty-eight (28) days after such notice is received (all references to "days" in this ADR provision are to calendar days). If the matter has not been resolved within twenty-eight (28) days after the notice of dispute, or if the parties fail to meet within such twenty-eight (28) days, either Party may initiate an ADR proceeding as provided herein. The parties shall have the right to be represented by counsel in such a proceeding.

1. To begin an ADR proceeding, a Party shall provide written notice to the other Party of the issues to be resolved by ADR. Within fourteen (14) days after its receipt of such notice, the other Party may, by written notice to the Party initiating the ADR, add additional issues to be resolved within the same ADR.

2. Within twenty-one (21) days following the initiation of the ADR proceeding, the Parties shall select a mutually acceptable independent, impartial and conflicts-free neutral to preside in the resolution of any disputes in this ADR proceeding. If the Parties are unable to agree on a mutually acceptable neutral within such period, each Party will select one independent, impartial and conflicts-free neutral and those two neutrals will select a third independent, impartial and conflicts-free neutral within ten (10) days thereafter. None of the neutrals selected may be current or former employees, officers or directors of either Party, its Subsidiaries or Affiliates or a current consultant or independent contractor of either Party or its Affiliates.

3. No earlier than twenty-eight (28) days or later than fifty-six (56) days after selection, the neutral(s) shall hold a hearing to resolve each of the issues identified by the Parties. The ADR proceeding shall take place at a location agreed upon by the Parties. If the Parties cannot agree, the neutral(s) shall designate a location other than the principal place of business of either Party or any of their Subsidiaries or Affiliates.

4. At least seven (7) days prior to the hearing, each Party shall submit the following to the other Party and the neutral(s):

(a) a copy of all exhibits on which such Party intends to rely in any oral or written presentation to the neutral;

(b) a list of any witnesses such Party intends to call at the hearing, and a short summary of the anticipated testimony of each witness;

(c) a proposed ruling on each issue to be resolved, together with a request for a specific damage award or other remedy for each issue. The proposed rulings and remedies shall not contain any recitation of the facts or any legal arguments and shall not exceed one (1) page per issue. The Parties agree that neither side shall seek as part of its remedy any punitive damages.

(d) a brief in support of such Party's proposed rulings and remedies, *provided*, that the brief shall not exceed twenty (20) pages. This page limitation shall apply regardless of the number of issues raised in the ADR proceeding.

Except as expressly set forth in subparagraphs 4(a) - 4(d), no discovery shall be required or permitted by any means, including depositions, interrogatories, requests for admissions, or production of documents.

5. The hearing shall be conducted on two (2) consecutive days and shall be governed by the following rules:

(a) Each Party shall be entitled to five (5) hours of hearing time to present its case. The neutral shall determine whether each Party has had the five (5) hours to which it is entitled.

(b) Each Party shall be entitled, but not required, to make an opening statement, to present regular and rebuttal testimony, documents or other evidence, to cross-examine witnesses, and to make a closing argument. Cross-examination of witnesses shall occur immediately after their direct testimony, and cross-examination time shall be charged against the Party conducting the cross-examination.

(c) The Party initiating the ADR shall begin the hearing and, if it chooses to make an opening statement, shall address not only issues it raised but also any issues raised by the responding Party. The responding Party, if it chooses to make an opening statement, also shall address all issues raised in the ADR. Thereafter, the presentation of regular and rebuttal testimony and documents, other evidence, and closing arguments shall proceed in the same sequence.

(d) Except when testifying, witnesses shall be excluded from the hearing until closing arguments.

(e) Settlement negotiations, including any statements made therein, shall not be admissible under any circumstances. Affidavits prepared for purposes of the ADR hearing also shall not be admissible. As to all other matters, the neutral(s) shall have sole discretion regarding the admissibility of any evidence.

6. Within seven (7) days following completion of the hearing, each Party may submit to the other Party and the neutral(s) a post-hearing brief in support of its proposed rulings and remedies, *provided*, that such brief shall not contain or discuss any new evidence and shall not exceed ten (10) pages. This page limitation shall apply regardless of the number of issues raised in the ADR proceeding.

7. The neutral(s) shall rule on each disputed issue within fourteen (14) days following completion of the hearing. Such ruling shall adopt in its entirety the proposed ruling and remedy of one of the Parties on each disputed issue but may adopt one Party's proposed rulings and remedies on some issues and the other Party's proposed rulings and remedies on other issues. The neutral(s) shall not issue any written opinion or otherwise explain the basis of the ruling.

8. The neutral(s) shall be paid a reasonable fee plus expenses. These fees and expenses, along with the reasonable legal fees and expenses of the prevailing Party (including all expert witness fees and expenses), the fees and expenses of a court reporter, and any expenses for a hearing room, shall be paid as follows:

(a) If the neutral(s) rule(s) in favor of one Party on all disputed issues in the ADR, the losing Party shall pay 100% of such fees and expenses.

(b) If the neutral(s) rule(s) in favor of one Party on some issues and the other Party on other issues, the neutral(s) shall issue with the rulings a written determination as to how such fees and expenses shall be allocated among the Parties. The neutral(s) shall allocate fees and expenses in a way that bears a reasonable relationship to the outcome of the ADR, with the Party prevailing on more issues, or on issues of greater value or gravity, recovering a relatively larger share of its legal fees and expenses.

9. The rulings of the neutral(s) and the allocation of fees and expenses shall be binding, non-reviewable, and non-appealable, and may be entered as a final judgment in any court having jurisdiction.

10. Except as provided in paragraph 9 or as required by law, the existence of the dispute, any settlement negotiations, the ADR hearing, any submissions (including exhibits, testimony, proposed rulings, and briefs), and the rulings shall be deemed Confidential Information. The neutral(s) shall have the authority to impose sanctions for unauthorized disclosure of Confidential Information.

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Isis Pharmaceuticals Singapore Pte Ltd., a Singapore Limited Private Company

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Regulus Therapeutics Inc., a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996) of Isis Pharmaceuticals, Inc. and the related Prospectus of our reports dated February 23, 2009, 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, 2008.

/s/ ERNST AND YOUNG

San Diego, California
February 23, 2009

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: February 26, 2009

/s/ STANLEY T. CROOKE

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

Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: February 26, 2009

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc. (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2008, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: February 26, 2009

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	*Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request**.**

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.