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, 2005

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

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

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

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

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

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

Large accelerated filer ☐ Accelerated filer x Non-accelerated filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ 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 National Association of Securities Dealers Automated Quotation National Market System was $174,075,233 as of June 30, 2005.*

The number of shares of voting common stock outstanding as of March 1, 2006 was 72,479,785.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Portions of the registrant's definitive Proxy Statement to be filed on or about March 22, 2006 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 3, 2006 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 72 to 77 incorporates several documents by reference as indicated therein.

* Excludes 13,007,479 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, 2005. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

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

TRADEMARKS

Affinitak™ is a trademark of Eli Lilly and Company.
Gemzar® is a registered trademark of Eli Lilly and Company.
Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Vitravene® is a registered trademark of Novartis AG.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company exploiting proprietary RNA-based drug discovery technologies to identify and commercialize novel drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins associated with disease. Interference with RNA can keep the body from producing the proteins that are involved in disease. We are the leader in making drugs that target RNA, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. In our Ibis division, we have developed a revolutionary system, called TIGER, that can, with a single test, simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. Additionally, as an innovator in RNA-based drug discovery and development, we are the owner or exclusive licensee of approximately 1,500 issued patents worldwide.

We successfully commercialized the first antisense drug, Vitravene. The rapid regulatory approval we received for Vitravene demonstrated our ability to meet Food and Drug Administration (FDA), and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs. We and our partners currently have 13 antisense drugs in preclinical and clinical development, the majority of which are in Phase 1 or Phase 2 human clinical trials. Our products in development address numerous therapeutic areas, including cardiovascular, metabolic, inflammatory and ocular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, such as oral and inhaled delivery, as well as infrequent dose administration. Our pipeline has matured to consist primarily of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs offer a number of advantages over first generation drugs. Specifically, second generation drugs offer the potential for improved safety and increased potency. In addition, because second generation drugs have a longer half-life, they have the potential to produce long-duration of therapeutic response and to support more convenient, less frequent dosing.

In 2005, we and our partners made important progress on all of our second generation drugs in development. In particular, we reported positive results from Phase 1 studies of ISIS 301012, our apoB-100 inhibitor for the lowering of high cholesterol, in which ISIS 301012 produced rapid, dose-dependent and prolonged reductions in apoB-100, low-density lipoprotein cholesterol, or LDL-C, and very low-density lipoprotein, or VLDL, total cholesterol and triglycerides, and was well tolerated. We initiated a Phase 2 development program of ISIS 301012 based on these positive results. Additionally, we reported data from a Phase 2 study in diabetic patients in which ISIS 113715, our PTP-1b inhibitor for the treatment of type 2 diabetes, improved glucose control, did not cause hypoglycemia and was well tolerated. Our partnered drugs in development also met important milestones. For example, OncoGenex Technologies Inc. initiated its Phase 2 development program of OGX-011 with four Phase 2 studies in prostrate, breast and non-small cell lung cancers and Eli Lilly and Company initiated Phase 1 studies of LY2275796, a cancer drug targeting eIF-4E, the second drug to enter the clinic from our research collaboration with Lilly.

Our Ibis division has invented technology that has the potential to revolutionize the identification of infectious diseases. We have applied this technology to develop the TIGER biosensor system, which can identify from a sample a broad range of infectious organisms without first needing to know what might be present in the sample. In 2005, our Ibis scientists advanced application development for the TIGER biosensor system through contracts with our government partners in the areas of biowarfare defense, epidemiological surveillance, microbial forensics and pharmaceutical process control. This work is valuable

because we can also apply much of this application development to non-government commercial opportunities. Further, this shift from technology development to application development under our government contracts reflects the progression from TIGER technology development to commercial viability.

Through our Ibis division, we plan to commercialize the TIGER biosensor system and application-specific infectious organism ID kits to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control, and infectious disease diagnostics. We began executing our commercialization plans for TIGER in 2005 by delivering two TIGER biosensor systems to our government partners, each for a different application. Our most recent delivery was to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics. Prior to that, we delivered a TIGER biosensor system to the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense. We plan to deliver TIGER biosensor systems to additional government customers in 2006. We also plan to begin shipping infectious organism ID kits in 2006.

As of December 31, 2005, we had earned $47.9 million in revenue from numerous government agencies relating to our Ibis division and we had an additional $8.4 million committed under our existing contracts and grants. These agencies include the Defense Advanced Research Projects Agency (DARPA), the Department of Homeland Security (DHS), the Centers for Disease Control (CDC), the Federal Bureau of Investigation (FBI), the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH).

We have a broad patent portfolio covering our products and technologies. We own or exclusively license approximately 1,500 issued patents, which we believe represents the largest and most valuable antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near term revenue and that we expect will also provide us with revenue in the future. The principal purpose of our intellectual property portfolio is to protect our products and those of our partners. Our intellectual property portfolio also enables us to expand our pipeline by granting to other companies limited access to antisense technology through licenses. Licensing partnerships include traditionally structured antisense drug discovery and development collaborations with large pharmaceutical companies like Eli Lilly and Company and Pfizer, Inc and satellite company partnerships, which we discuss below.

In addition, our intellectual property position and expertise in RNA-based therapeutics has repeatedly produced more opportunities than we can afford to develop on our own. As a result, we created a strategy to place these opportunities in the hands of partners who can enhance the opportunity with their own expertise and highly focused research and development efforts. In return, we share our expertise and intellectual property position in RNA-based therapeutics and take an ownership interest in the resulting products and/or partner company. Through these relationships, we can continue to expand the reach and potential of RNA-based therapeutics and potentially enjoy the success of multiple companies and products.

Because these companies work closely together with us, with the common goal of advancing the technology and/or pipeline, we refer to these companies as our satellite companies, and this strategy as our satellite company strategy. Our satellite company strategy allows us to create a much broader product pipeline than we could afford to develop on our own, while minimizing our financial obligations. Examples of these satellite companies include Achaogen, Inc., Alnylam Pharmaceuticals, Inc., Antisense Therapeutics, Ltd. (ATL), Ercole Biotech, Inc., iCo Therapeutics, Inc., OncoGenex, Rosetta Genomics, Inc., Santaris Pharma A/S and Sarissa, Inc.

Further, we have an active intellectual property licensing program in which we license aspects of our intellectual property to companies like Hybridon, Inc., Integrated DNA Technologies, Inc. (IDT), Roche Molecular Systems, atugen A/S, 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. In December 2001, we licensed several chemistry patents to Eyetech for the development of Macugen, a non-antisense drug for the treatment of wet age-related macular degeneration (AMD), that Eyetech is co-developing and commercializing with Pfizer. In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA, Inc., (DRC). In exchange for this sale, DRC paid us $7 million in October 2005 and agreed to pay us an additional $17 million over the next two years. As of December 31, 2005, we had generated more than $75 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

We incorporated in California in 1989, and in 1991 we reincorporated as a Delaware corporation. Our principal offices are in Carlsbad, California. We make available, free of charge, on our website, *www.isispharm.com*, our reports on 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*.

Drug Discovery and Development

Antisense 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 technology is different from traditional drug discovery because it interrupts the production of disease-causing proteins. We design our antisense drugs, or antisense inhibitors, to act earlier in the disease process than traditional drugs and to interrupt the production of disease causing proteins without disrupting proteins responsible for the body's normal functioning.

Genes contain the information necessary to produce proteins. A gene is made up of nucleotides: 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.

When a cell transcribes information from DNA 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 production 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. Antisense drugs can selectively inhibit one protein among a closely related group of proteins because antisense drugs interact with a specific RNA and not with the RNAs of other members of the group. It is easier to differentiate between closely related proteins at the RNA sequence level than by binding to the protein itself, as traditional drugs do. 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 mRNA receptor. With the completion of the human genome sequencing project, we now know the sequence for all potential mRNA targets in the human body.

We are the leader in the discovery and development of this exciting new class of therapeutic compounds. Our 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 compounds applicable to many disease targets. Further, over the past decade, our scientists have made great advances in chemistries, which we call our second generation antisense drugs. Second generation, including generation 2.2, antisense drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. Generation 2.2 antisense oligonucleotides are the same chemistry as second generation, but are better designed to exploit the RNase H mechanism. We have confirmed in animals that generation 2.2 antisense oligonucleotides

are significantly more potent than second generation. If these drugs display the increased potency in humans that we have observed in animals, our average dose will be decreased, reducing costs and enhancing therapeutic value. In addition, our generation 2.2 drugs may also be more commercially attractive as oral formulations. Our scientists have utilized our chemistry advancements to develop new formulations that expand the therapeutic and commercial opportunities of our pipeline. We and our partners are studying antisense drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, oral and topical formulations.

Approved Product and ProductsDrugs In Development

We successfully developed the first antisense drug to reach the market, Vitravene, for CMV retinitis, which is available through our partner, Novartis Ophthalmicss AG.

We have designed our drugs in development to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, and ocular and neurodegenerative diseases, and cancerinflammatory, metabolic, and cardiovascular and ocular diseases, and cancer, and we and our partners are studying them in intravenous, subcutaneous, aerosol, intravitreal, intrathecal, topical cream, enemacream, enema and oral formulations. Intravenous and subcutaneous formulations are commonly grouped together and referred to as parenteral forms of administration. The following table lists our approved product and each of our and our partners' productsdrugs under development, its target, disease indication and development status, as well as our commercial rights.

Isis Drugs in Development

Product(1)	Target	Potential Disease Indication(s)	Development Status(2)	Commercial Rights
Vitravene (I)	CMV	CMV Retinitis	Approved in the U.S. and Europe(3)	Isis/Novartis(3)
Alicaforsen (ISIS 2302) (E)*	ICAM-1	Ulcerative Colitis	Phase 2	Isis
ISIS 113715 (P)	PTP-1b	Diabetes	Phase 2	Isis
ISIS 301012 (P)	apoB-100	High Cholesterol	Phase 2	Isis
ISIS 369645 (A)	IL4R-a	Asthma/Rhinitis	Preclinical	Isis
ISIS 353512 (P)	CRP	Coronary Artery Disease	Preclinical	Isis
ISIS 333611 (IT)	SOD1	Amyotrophic Lateral Sclerosis	Preclinical	Isis(4)

Partner Drugs in Development

Product(1)	Target	Potential Disease Indication(s)	Development Status(2)	Commercial Rights
ATL 1102 (P)	VLA-4	Multiple Sclerosis	Phase 2	ATL
OGX-011 (P)	Clusterin	Cancer	Phase 2	OncoGenex/Isis
ATL 1101 (T)	IGF-1R	Psoriasis	Phase 1	ATL
LY2181308 (P)	Survivin	Cancer	Phase 1	Lilly
LY2275796 (P)	eIF-4E	Cancer	Phase 1	Lilly
iCO 007 (I)	c-Raf Kinase	Ocular Diseases	Preclinical	iCo
OGX-427 (P)	Hsp27	Cancer	Preclinical	OncoGenex

* Drugs based on our proprietary first-generation chemistry

(1) A = Aerosol; E = Enema; I = Intravitreal; P = Parenteral; T = Topical; IT = Intrathecal Infusion

(2) A drug in the preclinical phase of development is one in which we or our partners have made a decision to initiate toxicology and pharmacokinetic studies in animals to support the initiation of human clinical studies.

(3) Novartis has the exclusive worldwide rights to distribute Vitravene, which it distributes on a limited basis.

(4) The ALS Association is funding preclinical safety and efficacy studies of ISIS 333611.

The following section provides more detailed descriptions of our approved product and those drugs in development and the disease indications they target. We also have a significant research program.

Isis' Approved Product and Drugs in Development

Vitravene, or fomivirsen—In August 1998, the FDA approved Vitravene, an antisense drug that we discovered and developed, to treat CMV retinitis in AIDS patients. Novartis Ophthalmics AG, our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis currently offers Vitravene on a limited basis. Vitravene demonstrates our ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs.

Alicaforsen (ISIS 2302)—the most advanced compound in our inflammatory disease program selectively inhibits ICAM-1 gene expression. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, including inflammatory bowel disease. According to the Crohn's and Colitis Foundation of America, up to one million people have inflammatory bowel disease, with diagnoses evenly

split between Crohn's disease and ulcerative colitis, or UC. According to the European Federation of Crohn's and UC Associations, inflammatory bowel disease affects a similar number of people in Europe.

Ulcerative colitis (UC) is an inflammatory disease of the colon, a part of the large intestine. Inflammation and ulceration of the inner most lining of the colon characterize UC. Symptoms typically include diarrhea, rectal bleeding and abdominal pain. In December 2004, we released the results of three Phase 2 studies of alicaforsen enema to treat patients with UC in which alicaforsen enema produced significant and long-lasting disease improvement, as measured by changes in Disease Activity Index, or DAI, scores and other indicators of disease. In the Phase 2 studies alicaforsen enema outperformed both placebo and the enema standard of care. In particular, a substantial number of patients treated with alicaforsen enema experienced mucosal healing, as well as decreases in rectal bleeding and in stool frequency, manifestations of the disease that cause considerable discomfort, inconvenience and pain to patients. In all three trials, alicaforsen enema was well tolerated and improved signs and symptoms of disease in ulcerative colitis patients. In addition, data from a 2003 clinical trial for an enema formulation of alicaforsen demonstrated an improvement in clinical disease symptoms of up to nine months in patients with pouchitis. Pouchitis is an ulcerative colitis-like inflammation of the surgically constructed internal pouch created in ulcerative colitis patients when their diseased colons are removed.

Our goals for 2006 - 2007 for alicaforsen enema for ulcerative colitis are to partner it and prepare to initiate a Phase 3 program.

ISIS 113715—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. We believe that our second generation antisense drugs will have properties that will make them attractive therapies for metabolic diseases. According to the American Diabetes Association, diabetes affects more than 18 million people, with type 2 diabetes constituting about 90 percent of those cases.

ISIS 113715 is our second generation antisense inhibitor of the PTP-1b gene for the treatment of type 2 diabetes. ISIS 113715 represents a new approach to the treatment of diabetes. For years, pharmaceutical companies interested in treating diabetes have actively pursued phosphatases, such as PTP-1b, as targets in their traditional small molecule drug discovery efforts. However, due to structural similarities among closely related phosphatases, it has been difficult to identify small molecule drugs with sufficient specificity to be safe. Antisense technology allows us to design very specific drugs that inhibit PTP-1b and that do not inhibit other phosphatases.

Based on encouraging Phase 1 data, in which ISIS 113715 increased insulin sensitivity in normal volunteers, we initiated a Phase 2 clinical program to further evaluate the drug's ability to regulate blood sugar levels in patients with type 2 diabetes. In June 2005, we reported preliminary efficacy data from only the first two dose cohorts of our first Phase 2 study in diabetic patients. ISIS 113715 reduced HbA1C and plasma glucose after six weeks of dosing. In this ongoing Phase 2 monotherapy trial, ISIS 113715 improved glucose control in patients, did not cause hypoglycemia and was well tolerated.

Our goals for 2006 - 2007 for our ISIS 113715 clinical development program for type 2 diabetes are to:

- Report single agent Phase 2 data in patients with type 2 diabetes at the American Diabetes Association (ADA) meeting in June 2006;
  - Report final results demonstrating safety and activity after six weeks of treatment;
  - Report initial results demonstrating safety and activity after 12 weeks of treatment;
- Initiate a mechanistic study in patients with type 2 diabetes; and
- Initiate combination trials with other anti-diabetic agents.

ISIS 301012—We are pursuing the discovery and development of antisense drugs for the lowering of high cholesterol in routine patients and in patients with familial hypercholesterolemia (FH), a genetic disorder characterized by extremely high levels of lipids, and for the treatment of coronary artery disease. ISIS 301012 is a second generation drug that targets apoB-100, a molecule that has been of great interest to the industry, yet has long been considered "undruggable" by traditional small molecule approaches. ApoB-100 is a protein that plays a pivotal role in the production of low-density lipoprotein cholesterol, or LDL-C, and very low-density lipoprotein, or VLDL, the "bad" cholesterols.

- ***High Cholesterol***—According to the American Heart Association, cardiovascular disease is the leading cause of death in the United States. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Statistics from the American Heart Association show more than 100 million adults in the United States have high cholesterol levels. In preclinical studies, ISIS 301012 reduced total cholesterol, LDL-C, VLDL and triglyceride levels, all of which are keys to managing heart disease. In Phase 1 studies in normal volunteers with borderline elevated cholesterol, ISIS 301012 produced rapid, dose-dependent, and prolonged reductions in apoB-100, LDL, VLDL, total cholesterol and triglycerides.

  Recently, we reported data from a drug-drug interaction study in which ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. In this study and consistent with the growing body of data on ISIS 301012, the drug also reduced cholesterol and LDL-C, and was well tolerated. The results of this study support an important enhancement of the profile of ISIS 301012 through the use of ISIS 301012 in combination with statins or ezetimibe in treating patients with high cholesterol.

  In September 2005, we initiated the Phase 2 development program of ISIS 301012 in patients with high cholesterol. We are conducting a Phase 2 single-agent trial and a Phase 2 combination trial with statins. In both of these studies we are further evaluating the safety and efficacy of ISIS 301012 alone or in combination with statins and evaluating the dose and dose frequency to optimize both. We are also conducting Phase 2 studies of ISIS 301012 in patients with FH, a genetic disorder that causes extremely high cholesterol levels and results in early onset of heart disease, which we discuss below.

  In addition, in a Phase 1 study using an oral capsule formulation of ISIS 301012, one month of dosing in healthy volunteers resulted in an average of 6% bioavailability and statistically significant reductions in apoB-100, and commensurate reductions in LDL-C as compared to placebo. These results provide the basis for further improvements in formulations for oral delivery, particularly when combined with the advances demonstrated by generation 2.2 antisense oligonucleotides.

  Our goals for 2006 - 2007 for ISIS 301012 in patients with high cholesterol are to:

  - Report single agent Phase 2 data;
    - Demonstrate safety and activity as a single agent after three months of treatment;
    - Define dose and schedule for longer term studies;
  - Report Phase 2 combination studies;
    - Demonstrate safety and activity in combination with statins;
    - Define minimal effective dose and schedule as a combination agent;

- Initiate longer-term Phase 2 studies; and
- Continue to define profile upsides.

- ***Familial hypercholesterolemia (FH)***—FH is a dominantly inherited genetic condition that results in markedly elevated LDL cholesterol levels beginning at birth, and resulting in heart attacks at an

early age. There are two forms of FH, heterozygous (HeFH) and homozygous (HoFH). Patients with the disorder have consistently high levels of low-density lipoprotein, which leads to premature atherosclerosis of the coronary arteries. Typically, in men with HeFH, heart attacks occur in their 40s to 50s, and 85% of men with this disorder have experienced a heart attack by age 60, according to Medline Plus. The incidence of heart attacks in women with this disorder is also increased, but delayed 10 years later than in men. Patients with HoFH have cholesterol levels in excess of 600 mg/dL and develop waxy plaques beneath the skin over their elbows, knees and buttocks. These are deposits of cholesterol in the skin. In addition, they develop deposits in tendons and around the cornea of the eye. Atherosclerosis begins before puberty and heart attacks and death may occur before age 20.

As part of our ISIS 301012 Phase 2 development program, we recently initiated the development program of ISIS 301012 in patients with FH. The plan includes Phase 2 studies to evaluate the safety and efficacy of ISIS 301012 in patients with FH who are not achieving their cholesterol target levels on lipid-lowering therapy. These studies could lead to early registration of ISIS 301012 for patients with FH, potentially providing an accelerated pathway to commercialization, because of the unmet medical need for these patients.

Our goals for 2006 - 2007 for ISIS 301012 in patients with FH are to:

- Advance toward early commercialization in the 2008/2009 timeframe; and
- Demonstrate preliminary activity and safety in FH and define dose to support registration trials.

ISIS 369645—ISIS 369645 is our first drug for the treatment of asthma and related pulmonary diseases, and our first inhaled drug. ISIS 369645 is a second generation antisense inhibitor of the alpha subunit of the interleukin 4 receptor, IL4R-alpha. Inhibiting the production of IL4R-alpha inhibits the activity of two important cytokines in asthma, IL4 and IL13, which regulate inflammation, mucus overproduction and airway hyperresponsiveness. In preclinical studies, we have shown that a mouse-optimized antisense inhibitor of IL4R-alpha potently reduced IL4R-alpha: mRNA and protein levels, reduced lung cytokine production and inflammation, and airway hyper responsiveness in mouse models of asthma. In addition, these studies showed that, when delivered by inhalation, ISIS 369645 rapidly distributed to the airways and achieved therapeutic drug concentrations in multiple cell types with little systemic exposure. Based on these results, we initiated development activities for ISIS 369645.

ISIS 353512—ISIS 353512 is our first generation 2.2 antisense inhibitor. This drug targets C-reactive protein (CRP). Excessive amounts of CRP have recently been linked to coronary artery disease and a growing body of evidence from recent clinical trials implicates CRP in cardiovascular disease progression. These results further suggest that it may be therapeutically beneficial to significantly decrease CRP levels in patients who are at risk for coronary events. In preclinical studies, ISIS 353512 produced dramatic suppression of liver and serum CRP levels in monkeys. In additional studies, ISIS 353512 dramatically reduced human CRP levels in transgenic mice. Based on these results, we initiated development activities for ISIS 353512.

ISIS 333611—ISIS 333611 is our first drug for the treatment of neurodegenerative diseases to enter development. The drug will be administered by intrathecal infusion. In animal models, researchers have demonstrated that Isis' second generation drug, ISIS 333611, when delivered into the cerebral spinal fluid, inhibits Cu/Zn superoxide dismutase (SOD1), a molecule that is associated with an inherited, aggressive form of amyotrophic lateral sclerosis (ALS). Based on these findings, researchers from the Ludwig Institute, University of California, San Diego and from the Center for Neurologic Study, through funding from the ALS Association (ALSA), will conduct preclinical safety and efficacy studies of ISIS 333611.

Isis' Partnered Drugs in Development

ATL1102—ATL1102 is a second generation antisense inhibitor of CD49d, which is a subunit of Very Late Antigen-4, or VLA-4. Studies in animal models have demonstrated that inhibition of VLA-4 has a positive effect on a number of inflammatory diseases, including multiple sclerosis. In December 2001, we licensed ATL1102 to ATL. Under our agreement with ATL, we completed the required preclinical studies for ATL1102 and manufactured the drug for human clinical trials at ATL's expense. ATL is responsible for the clinical development and the commercialization of the drug. In June 2004, ATL announced the results of a Phase 1 clinical trial of ATL1102, in which the drug was well tolerated. In December 2004, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis. In March 2005, in light of the publicly announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL suspended the trial to convene an advisory group to consider the potential development path for ATL1102. In January 2006, ATL received approval to restart the Phase 2 trial for patients with relapsing-remitting multiple sclerosis. We plan to support ATL's development efforts to determine the potential of ATL1102 as an effective treatment for multiple sclerosis.

OGX-011—OGX-011 is a second generation antisense inhibitor of clusterin, which we are co-developing and commercializing with OncoGenex Technologies Inc., a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers. We designed OGX-011 to inhibit the secretory protein clusterin, which acts as a cell-survival protein that is over-expressed in response to tumor killing strategies, like chemotherapy, hormone ablation and radiation therapy. Based on analysis of human tumor tissue, clusterin is over-expressed in several cancers, including prostate, breast, renal, bladder, non-small cell lung and ovarian. By inhibiting clusterin, clinicians may be able to enhance the effects of drug therapies in the treatment of these cancers.

In a Phase 1 trial evaluating OGX-011 in combination with hormone ablation therapy prior to surgical removal of the prostate, OGX-011 was well tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91 percent dose-dependent reduction of its target, clusterin. In preclinical animal studies, scientists from both OncoGenex and Isis, in collaboration with the Prostate Center at Vancouver General Hospital, demonstrated that OGX-011 improved the potency of traditional chemotherapies more than ten-fold in prostate cancer, without compromising safety. These studies also demonstrated that OGX-011, when combined with other cancer treatments in preclinical model systems, may significantly improve tumor reduction and delay disease progression in prostate, lung, bladder and renal cancer. These findings support the continued development of OGX-011 in combination with standard chemotherapy and other agents. During 2005, OncoGenex initiated four Phase 2 clinical trials in prostate, breast and non-small cell lung cancer.

During 2006 - 2007, we plan to support OncoGenex's continued development of OGX-011 through the completion of the Phase 2 clinical trials in patients with lung, breast and prostate cancers. Based on patient accrual estimates, OncoGenex hopes to have response rates from the first of these Phase 2 trials by the end of 2006.

ATL1101—ATL1101 is an antisense compound targeting Insulin-like Growth Factor-I Receptor, or IGF-1R. Researchers believe that IGF-1R plays a pivotal role in the regulation of cell growth in psoriasis. ATL's scientists have demonstrated that antisense molecules delivered by intra-dermal injection successfully inhibit production of IGF-1R and normalize the skin architecture in human psoriasis skin samples grafted onto mice. In October 2005, ATL announced the results of its Phase 1 study in patients with psoriasis. In the study, ATL1101 demonstrated activity in psoriasis patients and was well tolerated. However, it was less effective than two currently marketed prescription medicines for the treatment of psoriasis, the reference points for the study. We plan to support ATL's program to explore the activity of ATL1101 in patients with psoriasis. According to the National Psoriasis Foundation, more than 4.5 million people in the United States have psoriasis, which is a non-contagious disorder of the skin, characterized by abnormal growth or overproduction of skin cells.

LY2181308—We licensed our preclinical anti-cancer candidate, LY2181308 to Lilly in 2002, as part of the expansion of our Lilly antisense drug discovery research collaboration into cancer, for which we earned $1.1 million. This drug continues to be part of our extended collaboration with Lilly to discover antisense drugs to inhibit specific gene targets associated with cancer. The drug targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin is one of the most highly 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.

In 2003, we earned a $1.5 million milestone payment from Lilly in the development of LY2181308. LY2181308 is the first drug from this partnership to advance to clinical trials. In November 2004, Lilly initiated Phase 1 clinical trials of LY218308 in cancer patients, for which we earned a second $1.5 million milestone payment. Lilly plans to initiate Phase 2 trials with LY218308 in cancer by the end of 2006.

LY2275796—LY2275796 is the second antisense anti-cancer drug we have licensed to Lilly and is currently in Phase 1 studies. During 2004, we earned a $750,000 license fee for this second generation antisense drug, which 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. Based on scientific literature, there is a strong indication that eIF-4E may act as a critical "switch" in cancer progression. In February 2006, Lilly initiated Phase 1 clinical trials of LY2275796 for which we earned a $750,000 milestone payment.

During 2006, we plan to support Lilly's ongoing anti-cancer antisense research and development programs through the progression of the Phase 1 clinical program of LY2181308 in patients with cancer and the Phase 1 clinical program of LY2275796 for cancer.

iCo 007—We licensed iCo 007 to iCo Therapeutics Inc. for the treatment of various eye diseases, such as diabetic macular edema (DME), diabetic retinopathy (DR) and age-related macular degeneration (AMD). iCo 007 is an antisense inhibitor of c-Raf kinase. In preclinical studies, antisense inhibition of c-Raf kinase was associated with a reduction in the formation and leakage of new blood vessels in the eye, suggesting c-Raf kinase inhibition could be valuable in the treatment of both DME, AMD and DR. AMD and DR are the leading causes of blindness in people over the age of 50 and in adults of working age (20-74) in industrialized countries, respectively.

OGX-427—OGX-427 is a second generation antisense inhibitor of heat shock protein 27. Higher levels of Hsp27 are detected in many cancers, including ovarian, breast and prostrate as well as in cancers of the blood and lymphatic system. In single agent pre-clinical studies, OGX-427 demonstrated significant anti-tumor activity at low concentrations. In addition, when combined with chemotherapy, in preclinical prostate cancer studies, OGX-427 was able to significantly enhance the anti-tumor activity of the widely used chemotherapy drug, paclitaxel. OncoGenex is currently conducting IND-enabling toxicology and pharmacokinetic studies for OGX-427 and OncoGenex anticipates that OGX-427 will enter clinical development in 2007.

Research Programs

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 backup compounds to our current drugs in development and to our development candidates.

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. Through these programs, we can efficiently explore numerous disease targets and identify lead compounds to advance into preclinical development. We are currently pursuing antisense drug discovery programs focused on various cardiovascular, metabolic and inflammatory disease targets, and cancer.

Additionally, we are pursuing three early-stage antisense mechanisms, including RNA interference, or RNAi, micro-RNA, and alternative splicing, through research collaborations and partnerships like those we have with Alnylam, Ercole and Rosetta Genomics.

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

Micro-RNAs are an emerging class of drug targets and a new area for drug discovery. Micro-RNAs are small RNA molecules that appear to have critical functions in controlling the process of gene expression. Micro-RNAs can serve as drug targets or as drugs themselves. Researchers estimate that there are more than 300 micro-RNA molecules in humans. We recently initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma.

Modulation of alternative splicing seeks to control the process by which a single gene can lead to several proteins. To be converted into proteins, genes must be initially copied into a pre-mRNA. Pre-mRNA often contains extra sequence information that must be removed prior to translation into the protein. This process is called splicing. Using antisense technology, we have been able to control how these stretches of RNA are spliced back together. This provides

another way to control the production of a disease-causing protein. Through our multi-year collaboration with Ercole, we are combining both companies' alternative splicing expertise to discover antisense drugs that regulate RNA splicing.

Ibis Division

How the TIGER Biosensor System Works

Within our Ibis division, we have invented technology that has the potential to revolutionize the identification of infectious diseases. We call this technology TIGER, which stands for Triangulation Identification for Genetic Evaluation of Risks. The TIGER biosensor system is a revolutionary system that can, with a single test, simultaneously, rapidly and accurately identify thousands of infectious organisms in a sample without needing to know beforehand what might be present in the sample. These organisms may be previously unknown, may have been genetically altered, or may be impossible to grow in the laboratory for identification through culturing.

Specifically, the TIGER biosensor system works by using our proprietary primers to look for unique DNA sequences in samples, weighs them with mass spectrometry, and compares the resulting weights against a database of organisms. This process allows the TIGER biosensor system to rapidly identify any of the many thousands of species of infectious organisms, as well as previously unknown agents, such as those that are bioengineered, that are in a sample. Once the analysis is complete, our proprietary software provides a simple, easy to read report that includes the organisms that are in the sample and the quantities of each organism present. In addition, the TIGER biosensor system can tell an investigator or physician if there is a previously unidentified organism in the sample and how it is related to organisms previously encountered. We have demonstrated the TIGER biosensor system can identify a variety of bacteria and viruses in both environmental and human clinical samples.

TIGER's ability to rapidly identify newly emerging organisms, down to the strain level, can provide public health officials and physicians with the critical information necessary to help track the spread of an infection, and ultimately, contain it. The TIGER biosensor system can also identify viruses, including mutated forms and previously unknown forms, which have the ability to outsmart traditional test methods. In addition, TIGER is able to identify co-pathogens associated with an infection, which are frequently present in rapidly spreading and severe infections. This information can allow physicians to effectively treat an infection with the potential not only to decrease mortality and morbidity, but also to contain the spread of infection.

TIGER Commercialization Strategy

Ibis' commercialization plan is a phased commercial development process that takes advantage of near-term opportunities, builds on an existing customer base and moves toward the larger healthcare markets. Through our Ibis division, we plan to commercialize the TIGER biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

The first phase of this commercialization plan involves selling TIGER biosensor systems and application-specific infectious organism identification test kits, or ID test kits, to government markets for biowarfare defense, epidemiological surveillance and forensics. We have already begun this first step in our commercialization plan for TIGER by delivering two TIGER biosensor systems to our government partners, each for a different application. We delivered our first TIGER biosensor system to USAMRIID for use in biowarfare defense. Our most recent delivery was to the DHS's National Bioforensic Analysis Center for use in microbial forensics. Our Ibis scientists are developing applications for epidemiological surveillance under a contract with the CDC and expect to deliver a TIGER biosensor system to the CDC later this year. In addition, we are currently working with the Naval Health Research Center using the TIGER biosensor system in respiratory disease surveillance and have analyzed hundreds of samples on the TIGER system at our facility. We plan to move the system hardware to the Navy's new laboratory facility, when it is finished. Because these government agencies provided funding for the development of the TIGER biosensor system, we provide the initial products as part of our ongoing government contracts. However, after the contract amounts are met, we expect our government customers to continue to purchase infectious organism ID kits to use with their TIGER biosensor systems.

We have begun the second phase of our commercialization plan to develop and commercialize TIGER biosensor systems and related products, and sell these products to customers in pharmaceutical process control and hospital-associated infection control markets. Under a contract from the NIAID, we are developing TIGER applications to assure the safety of biological drug products, including the development of protocols and procedures for vaccine screening that provide meaningful, relevant information to regulatory agencies and vaccine manufacturers on how to adequately assess the risk of infection in vaccines produced in new cell substrates. Additionally, we continue to work with government and non-government collaborators to develop applications to identify and track infectious organisms that cause hospital-associated infections. Hospital-associated infections, also known as nosocomial infections, include sepsis, urinary tract infections, pneumonia, and infections after surgery and are contracted after entering the hospital.

The third phase of our commercialization plan builds on the successes of our earlier phases. We plan to develop TIGER applications in the more regulated infectious disease diagnostic markets. When we enter the infectious disease diagnostic market, we expect to enter it in stages. First, we plan to develop infectious organism ID kits for difficult to diagnose and potentially lethal infectious diseases for which there are no relevant current technologies. As we gain experience and acceptance with these products, we will then move to diseases where there are existing diagnostic methods, which we will need to displace.

We plan to focus on the high-volume, high-margin consumables opportunity through the sale of infectious organism ID kits and related products to our customers. Although we will assemble instruments for our initial customers, we plan to transition the manufacturing, sales and support of the TIGER biosensor systems to an instrument manufacturer. In this way, we will limit our investment in instrument design and service, which can be done better by companies already in the instrument business. We believe we will need limited investment to create the infrastructure to make and sell infectious organism ID kits.

Continued Development Activities

Our Ibis division will continue to further develop the TIGER technology and applications through its contracts with government agencies, including DARPA, DHS, the CDC, the FBI and the NIAID, a part of NIH. Each of these agencies represents a significant source of funding for our TIGER program. As

of December 31, 2005, we had earned $47.9 million in revenue under our government contracts and grants, and we had an additional $8.4 million committed under our existing contracts and grants. We may receive continued funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of additional contract options by the contracting agencies. These agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

During 2005 and 2004, revenue generated from agencies of the United States Government totaled 30% and 28%, respectively, of our total revenue. Please refer to Note 7, "Segment Information and Concentration of Business Risk," starting on page F-37 of this report on Form 10-K for additional information about our Ibis division.

Our 2006-2007 goals for our Ibis division are to:

- Continue growth in revenue;
- Deliver additional TIGER biosensor systems;
- Complete an instrument strategic alliance;
- Ship infectious organism ID kits to customers;
- Continue development of specific ID kits for infectious organisms, and
- Build internal commercial and manufacturing organizations.

Collaborative Arrangements and Licensing Agreements

Our strategy is to use alliances with other companies and equity-based financing to increase our financial resources, reduce risk, and retain an appropriate level of ownership of products currently in development. Through alliances with major pharmaceutical companies and biotechnology companies, we can obtain funding, expand existing programs and gain additional expertise in developing and marketing products.

Our expertise and intellectual property position in RNA-based therapeutics has repeatedly produced more opportunities than we can afford to develop on our own. As a result, we created a strategy to place these opportunities in the hands of partners who can enhance the opportunity with their own expertise and highly focused research and development efforts. In return, we share our expertise and intellectual property position in RNA-based therapeutics and take an ownership interest in any resulting products and/or the partner company. Through these relationships, we can continue to expand the reach and potential of RNA-based therapeutics and enjoy the potential success of multiple companies and products.

Because these companies work closely together with us, with the common goals of advancing the technology and/or pipeline, we refer to these companies as our satellite companies, and this strategy as our satellite company strategy. Our satellite company strategy allows us to create a much broader product pipeline than we could afford to develop on our own, while reducing our financial obligations.

These satellite companies generally fall into two categories. The first category includes companies that in-license a drug product discovered by Isis, and agree to continue developing the product. Examples of these types of product-based satellite companies include Achaogen, ATL, iCo, OncoGenex, and Sarissa. The second category includes companies that are focused on a particular approach to RNA-based therapeutics, such as siRNA motifs or alternative splicing. These collaborations typically involve a cross-license between us and our partner so that each party has access to technology that is useful or necessary to advance the particular approach. This strategy allows us to keep abreast of newly emerging approaches to RNA-based therapeutics and augment our active programs in these areas. In addition, this structure allows us to reduce costs and share some of the risks involved in developing new technologies. Examples of these types of technology-based satellite companies include Alnylam, Ercole, Rosetta Genomics and Santaris.

2005 and Recent Collaboration and Licensing Highlights

We are focused on establishing new partnerships and on advancing and building upon existing relationships. We currently have agreements with more than a dozen partners. These span the three key areas of our business: antisense drug discovery and development, our Ibis division, and our intellectual property estate. The following is a list of our collaboration and licensing highlights for 2005 and early 2006.

We continue to expand our drug discovery and development programs and capitalize on our extensive patent estate through a combination of corporate partnerships, satellite company relationships and licensing transactions. During 2005 and recently, we announced several important achievements demonstrating the successful execution of this partnering strategy.

Collaborations

Eli Lilly and Company

- Lilly continues to conduct Phase 1 clinical trials of LY2181308 in cancer patients. LY2181308 is the first antisense drug to emerge from our joint research collaboration.
- Lilly initiated clinical trials of LY2275796 in cancer patients. This is the second anti-cancer antisense drug that Lilly has taken into the clinic. Lilly paid us a $750,000 milestone payment as a result of advancing LY2275796 into clinical trials.
- We extended our four-year drug discovery collaboration with Lilly to continue to advance the two anti-cancer antisense drugs, LY2181308 and LY2275796, identified during the initial collaboration and to continue our efforts to develop and refine antisense technologies.

Pfizer, Inc

- We earned $2.2 million in upfront fees and milestone payments in connection with a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease.

Satellite Company Relationships

Our satellite company relationships exemplify an important part of our partnering strategy in which we identify high quality biotechnology companies with which to closely collaborate to advance drugs and technologies.

OncoGenex Technologies Inc.

- OncoGenex initiated four Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancers.
- We expanded our antisense drug discovery and development collaboration in cancer for the development of OGX-427 and one additional second generation antisense anti-cancer drug.
- OncoGenex is currently conducting IND-enabling toxicology and pharmacokinetic studies for OGX-427. OncoGenex anticipates that OGX-427 will enter clinical development in 2007.

Antisense Therapeutics Ltd.

- ATL reported results from a study of ATL1101 in patients with psoriasis. ATL1101 demonstrated activity in psoriasis patients and was well tolerated.
- ATL received approval to restart the Phase 2 trial of ATL1102 for patients with relapsing-remitting multiple sclerosis.

Alnylam Pharmaceuticals, Inc.

- We received $3.7 million from Alnylam associated with the inclusion of our technology in Alnylam's collaboration with Novartis.

iCo Therapeutics, Inc.

- We licensed iCo 007 to iCo for the treatment of various eye diseases such as diabetic macular edema, age-related macular degeneration and diabetic retinopathy.

Achaogen, Inc.

- We licensed our proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens, for $1.5 million paid in Achaogen stock.

Sarissa, Inc.

- We licensed an antisense inhibitor of thymidylate synthase (TS), a drug target that protects cancer cells from the effects of several chemotherapy treatments, to Sarissa.

Rosetta Genomics, Inc.

- We entered into a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma.

Licensing Transactions

- We received $7 million from Drug Royalty USA, Inc. (DRC) as a partial payment for the acquisition of a part of our royalty rights in Macugen.

Ibis Division

Our Ibis division met major business milestones and continued applications development with government funding.

- We executed our commercialization plans by delivering the first two TIGER biosensor systems to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics and to the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense.
- We continued to increase revenue from government contracts and received additional government contracts and grants in 2005 for approximately $11.2 million from several government agencies to support the initial operations of the TIGER biosensor system and to continue advancing application development.

Antisense Drug Discovery Collaborations

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly, which included four key components.

- Lilly purchased $75.0 million of our common stock at $18 per share.
- We licensed to Lilly rights to Affinitak, which Lilly decided to discontinue funding.
- We entered into a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases and a related gene functionalization and target validation collaboration to determine the function of up to 1,000 genes.
- Lilly provided us a $100 million loan to fund our obligations under the research collaboration.

In August 2005, we extended the research collaboration with Lilly for approximately 24 months to focus on a select number of targets. During the extension, we and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue our efforts to develop and refine antisense technologies. During the extension, we will use collaboration funds to support our scientists and Lilly will support Lilly scientists.

- *LY2181308*—As part of the collaboration, Lilly licensed LY2181308, our antisense inhibitor of survivin, in 2002. To date, we have earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308, including the $1.5 million milestone payment we earned

when Lilly initiated Phase 1 clinical trials of LY2181308. We will receive additional milestone payments aggregating up to $25.0 million if LY2181308 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.

- *LY2275796*—Lilly also licensed LY2275796, an antisense inhibitor of eIF-4E, which was discovered through the research collaboration. We earned a $750,000 payment from Lilly for the license. In January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment. We will also receive additional milestone payments aggregating up to $19.5 million if LY2275796 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.
- *STAT-3*—As part of the recent collaboration extension, we are exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. We are working closely with Lilly to advance an improved STAT-3 candidate into development. We will receive milestone payments of up to

$28.0 million as an antisense drug targeting STAT-3 advances through various stages of development, and royalties on future product sales of this drug.

- *Antisense Drug Discovery*—The extended collaboration provides Lilly access to our patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, we and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries.

In connection with the extension, we converted the $100 million loan that Lilly previously provided to us into 2.5 million shares of our common stock. In connection with the extension and the conversion, Lilly agreed not to sell the conversion shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestone payments and royalties in the event of a stock price decline.

Our relationship with Lilly historically provided several revenue sources, including research funding related to the $100.0 million research loan, development milestones similar to the milestones for LY2181308 and LY2275796, and revenue related to Affinitak. During 2005, 2004 and 2003, we generated revenue from our relationship with Lilly totaling $10.8 million, $15.7 million, and $30.9 million, respectively, which comprised 27%, 37%, and 62%, respectively, of our total revenue during those same periods.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered a collaboration agreement with the Ludwig Institute, the Center for Neurologic Study (CNS) and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

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. Under the terms of the agreement, we received a technology access fee of $1.0 million. To date, we have earned milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay us additional milestone payments if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, we will earn milestone payments totaling up to $25.6 million. In addition, we will receive royalties on the sale of drugs resulting from the collaboration.

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 are used to treat serious bacterial infections. The program we licensed to Achaogen resulted from research conducted in our Ibis division to identify drugs to treat antibiotic-resistant infections.

In exchange for the exclusive, worldwide license to our aminoglycoside program, Achaogen issued to us $1.5 million of Achaogen Series A Preferred stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, we will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, we will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

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 $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. In addition, Alnylam and we will share the proceeds of any licenses Alnylam grants under its previously announced Interfe*Rx* program that include sublicenses to our patents. We agreed to provide Alnylam with access to our resources for development and commercialization of RNAi therapeutics, including process development, bioanalytic methods, quality control and manufacturing. We also made a $10.0 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the

target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties. For each drugs, the potential milestone payments to Alnylam total $3.4 million and are payable by us upon the occurrence of specified development and regulatory events. As of December 31, 2005, we did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery. For example, in October 2005 we earned $3.7 million from Alnylam associated with the inclusion of our technology in Alnylam's collaboration with Novartis. In addition, we have the potential to earn additional revenue in the form of milestones and royalty payments on drugs which utilize our technology sub-licensed by Alnylam to Novartis. In the second quarter of 2004, we earned a $500,000 license fee from Alnylam associated with the inclusion of our technology in Alnylam's ocular alliance with Merck.

In October 2004, we and Alnylam expanded our strong intellectual property positions in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of microRNA from the Max Planck Society. In September 2005 we and Alnylam co-exclusively licensed intellectual property for a microRNA gene involved in hepatitis C virus from Stanford University.

In September 2004, we recorded a non-cash loss on investment of $5.0 million related to the impairment of our equity investment in Alnylam. The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which we believe was primarily a result of financial market conditions

related to biotechnology companies. Alnylam's stock is currently trading significantly above its 2004 levels, which we believe reflects Alnylam's leading position in the field of RNAi. During the second half of 2005, we sold a portion of our Alnylam stock resulting in net proceeds of $2.6 million. We still hold more than 580,000 shares of Alnylam's stock.

During 2005 and 2004, we generated revenue from our relationship with Alnylam totaling $3.7 million and $5.5 million, respectively, representing 9% and 13%, respectively, of our total revenue.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to Antisense Therapeutics Limited, an Australian company publicly traded on the Australian Stock Exchange. We were responsible for completing the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug. In June 2004, ATL announced the results of a Phase 1 clinical trial of ATL1102, in which ATL1102 was well tolerated. In December 2004, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis. In light of the publicly announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL suspended the trial in March 2005 to convene an advisory group to consider the potential development path for ATL1102. In January 2006, ATL received approval to restart the Phase 2 trial for patients with relapsing-remitting multiple sclerosis.

ATL is also developing ATL1101, an antisense drug targeting IGF-1R for the treatment of psoriasis. ATL recently initiated a Phase 1 study of ATL1101. In October 2005, ATL announced the results of its Phase 1 study in patients with psoriasis. In the study, ATL1101 demonstrated activity in psoriasis patients and was well tolerated. However, it was less effective than two currently marketed prescription medicines for the treatment of psoriasis, the reference points for the study.

In addition, we are participating with ATL in a five-year antisense drug discovery and development collaboration. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide them during the collaboration. Additionally, ATL will pay to us royalties on any antisense drugs discovered and developed within the partnership. We currently own approximately 11% of ATL's equity and hold options for additional shares. If all of ATL's outstanding options, including ours, were exercised, our ownership in ATL would be approximately 14%.

Ercole Biotech, Inc.

In May 2003, we and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Part of this collaboration includes a cross-license of our respective splicing-related intellectual property with Ercole. We are combining our alternative splicing expertise with Ercole to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, we granted Ercole a license to our Bcl-x molecule and certain of our chemistry patents. In addition, we took an equity ownership position in Ercole with the initial funding, in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. We also have the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, we made cash payments to Ercole of $500,000 and $250,000, respectively, in exchange for a convertible note. We expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement.

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 age-related macular degeneration and diabetic retinopathy. iCo paid us a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note, which will convert into iCo stock upon iCo's completion of a qualified financing. iCo will pay us milestone payments totaling up to $23.2 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 2005, we entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by us for $700,000. iCo made a $525,000 prepayment to us consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug.

OncoGenex Technologies Inc.

In November 2001, we established a drug development collaboration with OncoGenex Technologies Inc., 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. We share in the costs of developing OGX-011. In exchange, we share in any revenue generated by OncoGenex for OGX-011. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target clusterin, with our proprietary second generation antisense chemistry. We conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. We also manufactured OGX-011 for preclinical and Phase 1/2 studies. OncoGenex performed Phase 1 clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and in combination with standard chemotherapy in patients with solid tumors known to express clusterin, including non-small cell lung, prostate, breast, renal, and ovarian cancers. In a Phase 1 trial evaluating OGX-011 in combination with hormone ablation therapy prior to surgical removal of the prostate, OGX-011 was well tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91 percent dose-dependent reduction of its target, clusterin. During the second half of 2005, OncoGenex initiated four Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancer. We plan to support OncoGenex's continued development of OGX-011.

In September 2003, we and OncoGenex expanded our antisense drug development partnership to include the development of the second generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug. OncoGenex issued us 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 pay us royalties on product sales. As of December 31, 2005, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, we further broadened our antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid us an upfront fee with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs.

As of December 31, 2005, our ownership interest in OncoGenex was less than 10%.

Rosetta Genomics, Inc.

In January 2006, we initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

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

In November 1998 and September 2000, we entered into license agreements with Santaris, formerly Pantheco. We amended and restated the agreements in May 2003. Under the terms of the amended and restated license agreement, we licensed our novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to our approval. Santaris has agreed to pay us royalties on any products developed under the license.

As part of our original license agreements with Pantheco, we received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, we purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock. After the merger and as of December 31, 2005, our ownership interest in Santaris was less than 10%.

Sarissa, Inc.

In February 2005, we licensed an anti-cancer antisense drug to Sarissa, Inc., a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Under the terms of the agreement, Sarissa paid us a $1.0 million upfront fee in exchange for the exclusive, worldwide license to the TS antisense drug. Sarissa paid the upfront fee with a convertible note, which will convert into Sarissa stock upon Sarissa's successful completion of a venture capital financing. Sarissa will also pay us milestone payments totaling up to $5.5 million for the achievement of clinical and regulatory milestones. In addition, we will receive royalties on any sales of the TS antisense drug. Sarissa is solely responsible for preclinical and clinical development of the drug.

Ibis Collaborations

To develop the TIGER biosensor system and applications, our Ibis division has received contracts and grants from a number of government agencies, including DARPA, DHS, the CDC, the FBI and NIAID, a part of the NIH. Each of these agencies represents a significant source of funding for our TIGER program. As of December 31, 2005, we had earned $47.9 million in revenue under our government contracts and grants. Also, we had an additional $8.4 million committed under our existing contracts and grants. In 2005, we advanced application development for the TIGER biosensor system through contracts with our government partners in the areas of biowarfare defense, microbial forensics, epidemiological surveillance and pharmaceutical process control.

Biowarfare Defense

The earliest application of our TIGER biosensor system to be funded by the government focused on bioweapons detection. In March 2004, Ibis received a two-year contract to further develop our TIGER biosensor system to identify infectious agents in biological warfare attacks from DARPA under a subcontract from SAIC. As part of this program, we successfully demonstrated proof-of-principle of the TIGER biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, we delivered our first TIGER biosensor system to USAMRIID for use in biowarfare defense.

Microbial Forensics

Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through an award from the FBI, Ibis is continuing its ongoing development of the Microbial Rosetta Stone (MRS) informational databases on microbial agents. The MRS program is a database of biological threat agents, their DNA sequences and effects, that law enforcement officials can use to confer deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis deployed its second TIGER biosensor system to the DHS's National Bioforensic Analysis Center for use in microbial forensics.

Epidemiological Surveillance

We continue to develop with our government partners applications for our TIGER biosensor system to rapidly identify, monitor and control infectious diseases. Specifically, in August 2005 we received a three-year grant worth up to $4.9 million from the NIAID, a part of the NIH. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections using the TIGER biosensor system. In addition, in September 2003, we received a three-year grant for up to $6.0 million from the CDC to develop and apply our TIGER technology to the surveillance of human infectious disease in the United States. We expect to deploy a TIGER biosensor system to the CDC later this year under this contract. In addition, we are currently working with the Naval Health Research Center using the TIGER biosensor system in respiratory disease surveillance and have analyzed hundreds of samples on the TIGER system at our facility. We plan to move the system hardware to the Navy's new laboratory facility, when it is finished.

Pharmaceutical Process Control

Government agencies such as the NIAID have engaged Ibis to develop applications to improve the safety of biological pharmaceutical products, such as vaccines. In 2004, we received funding from the NIAID to develop a TIGER application to specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates. We hope the applications we develop and validate under these government programs will create a new commercial prospect for our TIGER biosensor system in the area of pharmaceutical process control.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Hybridon, Inc.

In May 2001, we entered into an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to our suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, we paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in our common stock before May 2003. In return for access to our patents, Hybridon agreed to pay us $6.0 million in Hybridon common stock before May 2004. In September 2001 and October 2001, we issued to Hybridon 357,143 shares of our common stock valued at $5.0 million and 500,000 shares of our common stock valued at $10.0 million, respectively. In May 2002, Hybridon issued to us 1,005,499 shares of its common stock valued at $1.3 million and paid us $700,000 in cash. In August 2002, Hybridon and we cancelled the remaining reciprocal financial obligations related to this agreement. The cancellation of the obligations resulted in a decrease to our carrying value for the license in the amount of $500,000. During 2004 and 2005, we sold all of our Hybridon stock for net proceeds of approximately $665,000.

Integrated DNA Technologies, Inc.

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

In addition, in December 2001 we established a long-term research-scale antisense inhibitor supply agreement with IDT. In this supply agreement IDT agreed to manufacture research-scale antisense inhibitors and research reagents to our specifications. We paid IDT $5.0 million toward our future purchase of antisense inhibitors. During 2004, we recorded a non-cash charge of $4.2 million to write off the unused portion as part of our restructuring activities.

Out-Licensing Arrangements; Royalty Factoring Agreements

Drug Royalty Corporation

In December 2004, we sold a portion of our royalty rights in Macugen to DRC. In exchange for this sale, DRC paid us $7 million in October 2005 and agreed to pay us an additional $17 million over the next two years. Under the terms of the agreement, we and DRC will share the royalty rights on Macugen through 2009. After 2009, we retain all royalties for Macugen under our Eyetech agreement described below. Under the agreement, through 2009 DRC will receive the royalties on the first $500 million of annual sales of Macugen. We and DRC 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 $1.0 billion and 100 percent of all royalties after 2009. We have retained all milestones payable to Isis by Eyetech under the license agreement.

As part of the sale, we agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten per cent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to us through the default date minus the total of any royalties received by DRC through the default date. To

date, DRC has received royalties of $3.7 million. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, we fail to meet a minimum liquidity requirement equal to the then outstanding balance on our loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus our cash burn over the most recent three months. As collateral for our obligations under the sale agreement, we granted DRC a first priority security interest in the patents licensed by us to Eyetech under the license agreement and in the license agreement itself.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech Pharmaceuticals, Inc., 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 $2.0 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 $4.0 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication.

Roche Molecular Systems

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

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 capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide compounds, 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 compounds. 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 compounds. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions. For example, in November 2004, we and Nitto Denko Corporation announced that we had jointly developed a new high performance solid support for the manufacture of oligonucleotides. The new solid support has the potential to decrease manufacturing costs because it is less expensive than currently used solid supports and it has the potential to increase yield, thereby further reducing costs.

As part of our relationship with Lilly, in 2002 we upgraded and expanded our manufacturing facility, including the addition of a new state-of-the-art manufacturing suite. Lilly provided us with $21.2 million in funding to build the new suite. We can use this facility to manufacture drugs for ourselves and our partners.

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.

We have contractual obligations to manufacture clinical trial materials and/or commercial supply for ATL, iCo, Lilly, Novartis and OncoGenex. 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 compounds at commercially competitive prices.

Ibis Division

We plan to focus on the high-volume, high-margin consumables opportunity through the sale of infectious organism ID kits and related products to our customers. Although we will assemble instruments for our initial customers, we plan to transition the manufacturing, sales and support of the TIGER biosensor systems to an instrument manufacturer. In this way, we will limit our investment in instrument design and service, which can be done better by companies already in the instrument business. We believe we will need limited investment to create the infrastructure to make and sell infectious organism ID kits.

Patents and Proprietary Rights

Patents and Proprietary Rights

Our success will depend, in part, on our ability to obtain patent protection for our products in the United States and other countries. We file applications, as appropriate, for patents covering our products and processes. As of March 3, 2006, we owned or exclusively licensed approximately 1,500 issued patents worldwide. Patents issued to us, applied for by us or exclusively licensed to us, cover the following types of inventions, processes and products:

- Oligonucleotide chemical modifications covering core chemically-modified oligonucleotide building blocks, and oligonucleotides incorporating the same, which are useful in antisense drug design (including siRNA) as well as other oligonucleotide drugs such as aptamers;

- Antisense drug design, or chemical motifs, covering second generation, including generation 2.2, antisense drug design as well as other chemical motifs useful in other antisense applications;
- Methods of rapidly identifying antisense compounds targeted to particular RNA target sequences;
- Antisense drug compounds targeted to particular RNA target gene sequences and methods of using these antisense drug compounds to achieve certain therapeutic results;
- Methods of using antisense compounds in gene functionalization and target validation and mechanisms of action by which antisense inhibitors inactivate RNA targets;
- Methods for improved oligonucleotide drug manufacture, including processes for large-scale oligonucleotide synthesis;
- Novel formulations for oligonucleotide therapeutics;

- Methods and reagents for identifying unknown bioagents, bacterial, viral and fungal, using mass-spectrometry analysis. These cover our TIGER biosensor system and kits for various applications;
- Methods for optimizing the interaction of drug substances with their structured RNA target molecules. These cover mass spectrometry-based structural activity relationship discovery methods; and
- Anti-infective compounds, including aminoglycosides, derived from our mass spectrometry-based structural-activity relationship discovery methods.

Government Regulation

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

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.

In addition to regulations enforced by the FDA, 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.

We fund our Ibis division primarily through grants, contracts or subcontracts with agencies of the United States Government. As a result, we must comply with various government regulations, including the Federal Acquisition Regulations (FAR), and agency regulations supplemental to the FAR; the Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with certain contract negotiations; and laws, regulations and executive orders restricting the use and dissemination of information classified for national security purposes and the export of certain products and technical data. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations.

Competition

Drug Discovery and Development

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

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

of factors, including, among other things, product efficacy, safety, reliability, availability, price and patent position.

A number of factors have affected the market for Vitravene, our antisense drug for CMV retinitis. Anti-HIV drugs that were introduced prior to Vitravene's approval have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis.

Ibis Division

While Ibis has a unique technology, the markets for our technologies and products are very competitive, and we expect the intensity of competition to increase. Currently, we compete primarily with companies that are pursuing technologies and products that provide alternatives to ours. We are unaware of other technologies which have the ability to do the parallel analysis, quantification, and identification of the complete bacterial and viral genomes from a single sample.

Microorganism identification has traditionally relied on laborious culture-based and microscopy techniques. Automated versions of these methodologies using the growth or metabolic characteristics of an organism are now progressing towards the market; however, they still require that an organism be

culturable, and when the precise identity of an organism is in question, genotypic testing methods can provide more precise, and at times more rapid results. Emerging molecular-based approaches for the parallel detection of known infectious agents include multiplexed PCR methods and microarray strategies. With these methods, prior knowledge and assumptions about the type and strain of bacteria or virus guide the detection strategies, making them less amenable for the high-throughput detection of a broad spectrum of microorganisms or the detection of previously unknown or uncharacterized agents.

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

Employees

As of March 3, 2006, we employed approximately 258 individuals, nearly half of whom hold advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of March 3, 2006:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	60	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, J.D.	50	Director, Executive Vice President, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.	49	Senior Vice President, Research
David J. Ecker, Ph.D.	51	Vice President, Chief Scientific Officer of the Ibis Division
Arthur A. Levin, Ph.D.	52	Senior Vice President, Development
Michael J. Treble	59	Vice President, President of the Ibis Division
Mark K. Wedel, M.D., J.D.	59	Senior Vice President, Development and Chief Medical Officer

STANLEY T. CROOKE, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer

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

B. LYNNE PARSHALL, J.D.
Director, Executive Vice President, Chief Financial Officer, and Secretary

Ms. Parshall has served as a Director of Isis since September 2000. She has served as our Executive Vice President since December 1995, 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, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is on the Board of Trustees of the Bishops School and is also a member of the American, California and San Diego bar associations. Ms. Parshall has served on the Board of Corautus Genetics Inc. since May 2005 and of Cardiodynamics International Corp. since June 2005, both biopharmaceutical companies.

C. FRANK BENNETT, Ph.D.
Senior Vice President, 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.

DAVID J. ECKER, Ph.D.
Vice President, Chief Scientific Officer of the Ibis Division

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

ARTHUR A. LEVIN, Ph.D.
Senior Vice President, Development

Dr. Levin was promoted to Senior Vice President, Development in January 2006. From 1995 until January 2006 he served as our Vice President, Development. Prior to joining Isis, Dr. Levin worked at Hoffmann-La Roche Inc. where he was Research Leader in their Investigative Toxicology Department managing the Nuclear Receptor Research Group. During his tenure at Hoffman-LaRoche, Dr. Levin also established and supervised laboratories dedicated to the research of mechanisms of toxicity, biochemical toxicology and toxicokinetics.

MICHAEL J. TREBLE

Vice President, President of the Ibis Division

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

MARK K. WEDEL, M.D, J.D.

Senior Vice President, Development and Chief Medical Officer

Dr. Wedel joined Isis in 2001 and is responsible for clinical operations, strategic therapeutic portfolio management, and oversees all of Isis' development programs. Prior to joining Isis, he served as Director of Medical Affairs, Director of Pulmonary Therapeutics, and as a consultant for the United States Department of Justice in its Health Care Fraud Division. Prior to that, Dr. Wedel was the Medical Director of the Medical/Surgical Intensive Care Unit, Green Hospital of the Scripps Clinic and Research Foundation and the Attending Intensivist, responsible for the care and treatment of critically ill patients.

Item 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this report on Form 10-K, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of December 31, 2005, we had accumulated losses of approximately $770.8 million and stockholders' equity of approximately $2.7 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 interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. 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.

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

All of our product candidates are undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements at least through 2007. If we do not meet our goals to commercialize our products,

or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. In addition, if our stockholders do not approve an increase in our authorized capital stock, it may limit our ability to raise funds. 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, product candidates or products.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, 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. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

We have entered into collaborative arrangements with third parties to develop many of our product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;

- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future products.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. 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 outcome of both Phase 3 trials, Lilly discontinued its investment in Affinitak.

Other drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis division and the development of our TIGER biosensor system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical companies or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

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 drug and, as a result, could delay or otherwise negatively affect the commercialization of our drug.

In addition, the disappointing results of the two Affinitak trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trial failures 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.

If we cannot protect our patents or our proprietary rights, others may compete more directly 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.

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

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve

milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

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

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. 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. 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, 2005, the market price of our common stock ranged from $2.76 to $6.09 per share. On February 17, 2006, the closing price of our common stock on the Nasdaq National Market was $8.24. 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.

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

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

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

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

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

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights to Lilly, which cover approximately 2.5 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of warrants, which we issued as part of our August 2005 private placement. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. The addition of these shares into the 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 Securities and Exchange Commission, the Public Company Accounting Oversight Board (PCAOB), or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drug candidates, 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 before a drug can be approved for sale. We must conduct these trials in compliance with United States Food and Drug Administration 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, 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. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product 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 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, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease; the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials.

Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. 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 enough 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 trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

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 payers accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available 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 payers.

Based on the profile of our drugs, physicians, patients, patient advocates, payers 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 may be required to establish large-scale commercial manufacturing capabilities. 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 our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

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 or unique methods of identifying infectious organisms. Our competitors may succeed in developing drugs or technologies that are more effective than any drugs or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

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.

We depend on third parties in the conduct of our clinical trials for our product candidates 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 product candidates and expect to continue to do so in the future. 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 could delay or prevent the development, approval and commercialization of our product candidates.

Risks Associated with our Ibis Division

We may not successfully develop or derive revenues from our business based on our TIGER biosensor system.

Our TIGER biosensor system is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our TIGER biosensor system due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our TIGER business could fail to meet our business and financial objectives.

If we fail to secure commercial partners for our TIGER biosensor system, our commercialization efforts for our TIGER biosensor may be harmed or delayed.

We expect to depend on third parties to commercialize our TIGER biosensor system, particularly in the areas of manufacturing, selling and servicing the instruments. In addition, we expect to depend on third parties to sell and distribute our infectious organism ID kits to non-government customers in the healthcare-associated infection control and infectious disease diagnostic markets. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the TIGER biosensor system. We may not successfully establish a distribution, manufacturing, sale or service relationship or be able to make alternative arrangements. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our profit margins on our TIGER instruments and ID kits.

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

Virtually all of our TIGER business' revenue is from the sale of services and products to the United States government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, any of which could reduce our revenues and cash flows from U.S. government contracts. Our revenues and cash flow from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months and fiscal year ended December 31, 2005, Isis derived approximately 21% and 30%, respectively, of its revenue from agencies of the United States government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our United States Government contracts and subcontracts are simultaneously delayed or canceled for budgetary performance or other reasons. If United States defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

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

Under our agreements with the United States government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and Isis do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of our TIGER business. With respect to U.S. government

contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with the U.S. government. Among the most significant regulations are the following:

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

If our TIGER biosensor system's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

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

If we had to replace a supplier of one of the major hardware components of our TIGER biosensor system, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our TIGER biosensor system. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle.

If our TIGER business fails to compete effectively, it may not succeed or contribute significant revenues.

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

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

Improvements in preventing major diseases could reduce the need for our TIGER biosensor instruments and ID kits, which in turn could reduce our revenues.

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

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

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our TIGER biosensors systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our TIGER biosensors systems or services.

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

If we or our partners are required to obtain regulatory approval for our TIGER biosensor system applications, we may not successfully obtain approval.

Depending on their intended use, our TIGER biosensor systems may be regulated as medical device by the FDA and comparable agencies of other countries and require either premarket approval (PMA) or 510(k) clearance from the FDA, prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. We or our collaborators may encounter delays or rejections of potential products may be encountered based on changes in

regulatory policy for product approval during the period of product development and regulatory agency review.

Item 1 B. Unresolved Staff Comments

Not applicable.

Item 2. Properties.

As of March 3, 2006, we occupied approximately 173,000 square feet of laboratory and office space, including 6,888 square feet of manufacturing area built to meet Good Manufacturing Practices and 18,800 square feet, which our Ibis division occupies. We are primarily located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements, of which two leases will expire in 2007, the third will expire in 2010, and the fourth will expire in 2020. During 2005, as a part of our restructuring activities, we sold three buildings we previously owned resulting in a net gain of approximately $1.5 million. Isis leased back one of the properties it sold for an initial term of fifteen years.

Item 3. Legal Proceedings.

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, that purports to license certain intellectual property, including United States Patent No. 5,013,830, or the ‘830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the ‘830 patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. In October 2005, we filed our answering statement. We believe that Ajinomoto’s claims are without merit, and we intend to vigorously defend our position. Ajinomoto and Isis agreed to a bifurcated arbitration process in which the arbitrator first heard contract

arguments and will hear the patent arguments, if necessary, at a later date. The contract argument portion of the arbitration proceeding took place on February 22, 2006. We expect a ruling from the arbitrator on the first part of this proceeding in the middle of April 2006.

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 National 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 National Market. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW
2005		
First Quarter	$ 6.09	$ 3.76
Second Quarter	$ 4.29	$ 2.76
Third Quarter	$ 5.80	$ 3.75
Fourth Quarter	$ 5.41	$ 4.20
2004		
First Quarter	$ 9.59	$ 6.66
Second Quarter	$ 9.90	$ 5.54
Third Quarter	$ 6.67	$ 4.22
Fourth Quarter	$ 6.63	$ 4.25

As of March 1, 2006, there were approximately 1,029 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Recent Sales of Unregistered Securities

Not applicable.

Purchases of Equity Securities by Us and Affiliated Persons

Not applicable.

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

	Years Ended December 31,				
	2005	2004	2003	2002	2001
Consolidated Statement of Operations Data:					
Revenue (includes amounts for R&D, licensing and royalties)	$ 40,133	$ 42,624	$ 49,990	$ 80,179	$ 53,273
Research and development expenses	$ 82,467	$ 118,474	$ 116,963	$ 124,074	$ 83,741
Net loss applicable to common stock(1)	$ (72,401)	$ (142,864)	$ (95,690)	$ (73,302)	$ (75,131)
Basic and diluted net loss per share	$ (1.15)	$ (2.52)	$ (1.73)	$ (1.35)	$ (1.70)
Shares used in computing basic and diluted net loss per share	62,877	56,642	55,463	54,480	44,109

	Years Ended December 31,				
	2005	2004	2003	2002	2001
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 94,389	$ 103,883	$ 215,504	$ 289,353	$ 312,018
Working capital	$ 82,065	$ 82,193	$ 194,004	$ 244,230	$ 280,569
Total assets	$ 166,373	$ 208,425	$ 334,942	$ 438,683	$ 417,061
Long-term debt and capital lease obligations, less current portion	$ 139,915	$ 236,611	$ 213,397	$ 192,893	$ 125,710
Accumulated deficit	$ (770,848)	$ (698,447)	$ (555,583)	$ (459,893)	$ (386,591)
Stockholders equity (deficit)	$ 2,665	$ (72,133)	$ 67,178	$ 155,477	$ 223,099

(1) Our net loss applicable to common stock includes charges related to restructuring activities of $7.0 million, $32.4 million, $1.8 million, and $1.4 million in 2005, 2004, 2003, and 2002, respectively. During 2001, we did not incur any charges related to restructuring activities.

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

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and successfully turned our expertise into one marketed product and 13 antisense drugs, which we continue to advance in preclinical and clinical development with our partners. Most of these are in Phase 1 and Phase 2 human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including cardiovascular, metabolic, inflammatory and ocular diseases, and cancer. We and our partners are studying these drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, topical cream and oral formulations, and we use second generation chemistry to advance our antisense drugs.

In 2005, we and our partners made important progress on all of our second generation drugs in development. In particular, we reported positive results from Phase 1 studies of ISIS 301012, our apoB-100 inhibitor for the lowering of high cholesterol, in which ISIS 301012 produced rapid, dose-dependent and prolonged reductions in apoB-100, low-density lipoprotein cholesterol, or LDL-C, and very low-density lipoprotein, or VLDL, total cholesterol and triglycerides, and ISIS 301012 was well tolerated. We initiated a Phase 2 development program of ISIS 301012 based on these positive results. Additionally, we reported data from a Phase 2 study in diabetic patients in which ISIS 113715, our PTP-1b inhibitor for the treatment of type 2 diabetes, improved glucose control, did not cause hypoglycemia and was well tolerated. Our partnered drugs in development also met important milestones. For example, OncoGenex Technologies Inc. initiated its Phase 2 development program of OGX-011 with four Phase 2 studies in prostate, breast and non-small cell lung cancers and Eli Lilly and Company initiated Phase 1 studies of LY2275796, a cancer drug targeting eIF-4E and the second drug from our research collaboration.

We have a broad patent portfolio covering our technologies. We own or exclusively license approximately 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. As of December 31, 2005, we had generated more than $75 million from our intellectual property licensing program that helps support our internal drug discovery and clinical development programs.

In our Ibis division, we have developed a revolutionary system, called TIGER, that can, with a single test, simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. During 2005, our Ibis scientists advanced application development through contracts with our government partners in the areas of biowarfare defense, epidemiological surveillance, biological products screening and microbial forensics. This work has added value to us in that we can also apply much of this application development to non-government commercial opportunities. Further, this shift from technology development to application development under our government contracts reflects the progression from TIGER technology development to commercial viability.

Through our Ibis division, we plan to commercialize the TIGER biosensor system and infectious organism ID kits to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control, and infectious disease diagnostics. We began executing our commercialization plans for TIGER in 2005 by delivering two TIGER biosensor systems to our government partners, each for a different application. Our most recent delivery was to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics. Prior to that, we delivered a TIGER biosensor system to the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense. We plan to deliver TIGER biosensor systems to additional government customers in 2006. We also plan to begin shipping infectious organism ID kits in 2006.

Much of the development of our TIGER biosensor system and related applications has been funded through government contracts and grants. As of December 31, 2005, we had earned $47.9 million in revenue from numerous government agencies and we had an additional $8.4 million committed under our existing contracts and grants. These agencies include the Defense Advanced Research Projects Agency (DARPA), Department of Homeland Security (DHS), the Centers for Disease Control (CDC), the Federal Bureau of Investigation (FBI), the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and the National Institute of Allergy and Infectious Diseases (the NIAID), a part of the National Institutes of Health (NIH).

We pursue early-stage antisense research programs, including RNA interference (RNAi), microRNA, and alternative splicing through research collaborations and partnerships, similar to our strategic alliances with Alnylam Pharmaceuticals, Inc. (Alnylam), Ercole Biotech, Inc. (Ercole) and Rosetta Genomics, Inc.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. We continue to utilize our proprietary technology to discover and characterize novel antisense inhibitors through which our scientists modify the properties of our antisense drugs for optimal use with particular targets and thus, produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, our scientists have made significant advances in oligonucleotide chemistries, including what we call our second generation antisense drugs. Second generation, including generation 2.2, drugs provide increased potency, stability, oral bioavailability and improved side effect profile. We and our partners are studying antisense drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, oral and topical formulations.

Along with our partners we currently have 13 drugs in development, of which five are in Phase 2 clinical development, three are in Phase 1 clinical development and five are in preclinical development. Our partners are licensed to develop, with our support, seven of these 13 drugs, which substantially reduces our development costs.

Ibis Division. Our Ibis division has developed a revolutionary system, called TIGER, that can simultaneously identify thousands of infectious organisms in a sample, without needing to know beforehand what might be present in the sample. Ibis plans to commercialize the TIGER biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with the audit committee of our Board of Directors. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. 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 propriety of revenue recognition and associated deferred revenue;
- Determination of proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of proper valuation of inventory;
- Determination of appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determine 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 and the expected stock price volatility over the term of the expected life.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include Staff Accounting Bulletin No. 101, or SAB 101, *"Revenue Recognition in Financial Statements,"* SAB 104, *"Revenue Recognition,"* and Financial Accounting Standards Board Emerging Issue Task Force No. 00-21, or EITF 00-21, "*Accounting for Revenue Arrangements with Multiple Deliverables*."

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

We often enter into collaborations where we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with Antisense Therapeutics, Ltd. (ATL), Lilly and OncoGenex.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. As of December 31, 2004, we had drawn down $95.0 million on this loan. In March 2005, we drew down the final $5.0 million of the loan. In August 2005, we converted the loan into 2.5 million shares of our common stock.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated for future performance related to the achievement of the milestone. We recognized revenue during 2005 related to milestones achieved under our agreement with Pfizer, Inc.

We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. To date, in three 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 our obligation was complete under the terms of the manufacturing agreement in place and title had transferred to the customer before we recognized the related revenue.

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

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate 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.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, *"Accounting for Certain Investments in Debt and Equity Securities."* We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is 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. 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 2005, we did not record an impairment loss on our investments. In 2004, we recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of our equity investment in Alnylam Pharmaceuticals, Inc. (Alnylam). The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which we believe was primarily a result of financial market conditions related to biotechnology companies. Alnylam's stock is currently trading significantly above its 2004 levels, which we believe reflects Alnylam's leading position in the field of RNAi.

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*, or SFAS 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties to determine if any impairment is present. We consider the following factors:

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

In December 2004, we made a strategic decision to reorganize and focus our resources on our key programs. As a result, during the fourth quarter of 2004 we recorded charges of approximately $11.5 million related to the write-down of tangible and intangible assets, including equipment and patent costs that were non-essential to our current focus. We had additional write-downs of $14.2 million in 2005 associated with our restructuring activities, which were primarily related to the sale of three of our buildings.

Valuation of Inventory

We include in inventory 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 expense these costs when we deliver our drugs to partners, or as we use these drugs in 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 considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its net realizable value related to our decision to reorganize and focus our resources on key programs.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

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

Segment Information

We provide segment financial information and results for both our Drug Discovery and Development segment and Ibis division based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Pro forma Stock-Based Compensation

We provide pro forma net loss and loss per share amounts in accordance with the disclosure only provision of Statement of Financial Accounting Standards No. 123, *"Accounting for Stock-Based Compensation."* (SFAS No. 123). The stock-based compensation expense used in these pro forma amounts is based on the fair value of the option at the grant date, which uses the fair value pricing method described in SFAS No. 123. This method requires us to use

several assumptions to estimate the fair value, including the expected life of the option and the expected stock price volatility over the term of the expected life. Should any of these assumptions change or differ from the actual life or actual stock price volatility, our pro forma results could differ substantially.

Effective in 2006, pursuant to the provisions of SFAS No. 123(R), *"Share-Based Payment,"* we will be required to recognize as a charge to our statement of operations the fair value of all share-based payments to employees, including stock option grants. We cannot currently predict the impact that this new accounting treatment will have on our statement of operations because it will depend on levels of share-based payments we grant in the future. However, accounting for share-based payments to employees using the fair value method will have no impact on our overall financial position.

Results of Operations

Years Ended December 31, 2005 and December 31, 2004

Revenue

Total revenue for the year ended December 31, 2005 was $40.1 million, compared to $42.6 million for the same period in 2004. Our revenue frequently fluctuates based on the timing of activities under contracts. Significant components of 2005 revenue included $7.0 million from Drug Royalty USA, Inc. (DRC), as a partial payment for the acquisition of a part of our royalty rights in Macugen; approximately $3.7 million from Alnylam associated with the inclusion of our technology in its collaboration with Novartis; $2.7 million from OncoGenex for the expansion of the companies' cancer collaboration and the purchase of drug manufactured by us and $2.2 million from our ophthalmology collaboration with Pfizer. Revenue from collaborations was less in 2005 than in 2004 primarily due to a decrease in revenue associated with our collaboration with Lilly, which was extended in August 2005 to focus on a select number of targets. Our ability to maintain revenue at current levels will depend on our ability to obtain new revenue sources and expand existing revenue sources in 2006.

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

	Year Ended December 31,	
	2005	2004
Drug Discovery and Development:		
Research and development revenue	$ 16,817	$ 21,684
Licensing and royalty revenue	11,523	10,007
	$ 28,340	$ 31,691
Ibis Division:		
Research and development revenue	$ 11,793	$ 10,933
Licensing and royalty revenue	—	—
	$ 11,793	$ 10,933
Total revenue:		
Research and development revenue	$ 28,610	$ 32,617
Licensing and royalty revenue	11,523	10,007
	$ 40,133	$ 42,624

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Our revenue under the category of research and development revenue under collaborative agreements for the year ended December 31, 2005 was $16.8 million, compared to $21.7 million for the same period in 2004. Significant components of our 2005 research and development revenue included $2.2 million from our ophthalmology collaboration with Pfizer and $2.7 million from OncoGenex for the expansion of our cancer collaboration and the purchase of drug manufactured by us. The decrease of $4.9 million was primarily due to a decrease in revenue associated with our collaboration with Lilly.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $11.5 million for the year ended December 31, 2005, compared to $10.0 million for the same period in 2004. The increase of $1.5 million was primarily due to $7.0 million in payments from DRC, as a partial payment for part of our royalty rights in Macugen,

and approximately $3.7 million from Alnylam associated with the inclusion of our technology in its collaboration with Novartis, offset in part by $4.0 million of milestone payments related to Macugen that we earned from Eyetech and $5.5 million that we earned from Alnylam in 2004.

Ibis Division

Research and Development Revenue Under Collaborative Agreements

Our Ibis division generates research and development revenue from grants and contracts from United States government agencies, including DARPA, the CDC, the FBI, the DHS, and the NIAID, a part of the NIH. Our Ibis division generated revenue of $11.8 million for the year ended December 31, 2005, compared to revenue of $10.9 million for the same period in 2004. This increase from 2004 to 2005 was primarily a result of increased funding for internal labor under new and existing government contracts and reflects increased funding to pay for our applications development and technology advancement in support of our commercialization plans for TIGER. The increase from 2004 to 2005 was offset in part by a decrease in revenue earned from pass through equipment purchases. During 2004, Ibis acquired equipment at a cost of $3.2 million to build multiple TIGER biosensor systems. Because Ibis was

assembling the systems in 2005 for which it had purchased equipment in 2004, Ibis' equipment purchases during 2005 of $1.2 million were significantly lower than 2004 resulting in reduced revenue and associated expense in 2005 compared to 2004.

Operating Expenses

Total operating expenses were $97.3 million and $160.5 million for the years ended December 31, 2005 and 2004, respectively. We achieved a 39% decrease in our operating expenses in 2005 compared to 2004 principally through a reorganization in early 2005 that focused our resources on key programs. The cost savings we achieved through the reorganization led to a decrease in R&D and G&A expenses of $37.2 million. A decrease in primarily non-cash costs associated with restructuring activities, consisting principally of inventories, of $25.5 million from 2004 to 2005 also contributed to the reduction in operating expenses.

Total operating expenses for the years ended December 31, 2005 and 2004 included a non-cash compensation benefit of approximately $544,000 and $6,000, respectively, due to variable accounting for stock options. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation related to stock options as a result of the variability in the Company's stock price.

In order to analyze and compare our results of operations to similar companies, we believe that it is important to exclude compensation related to stock options from operating expenses because it is based on the variability of our stock price rather than operations, and exclude restructuring activities because these costs are directly related to isolated events.

Research and Development Expenses

For the year ended December 31, 2005, our total research and development expenses were $82.5 million, compared to $118.5 million for the same period in 2004. The substantial decrease of $36.0 million from 2004 to 2005 was primarily due to cost savings achieved as a result of our restructuring activities. These cost savings included significant reductions in personnel, lab supplies and facilities costs as well as reductions in third party clinical development costs attributed to our decision to focus our research and development resources on our most promising second generation drugs and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis division, and R&D support costs. As part of our corporate restructuring in early 2005, we consolidated our research manufacturing functions and our drug manufacturing functions into a

combined manufacturing group that can serve the needs of both antisense drug discovery and antisense drug development. We call this new function Manufacturing and Operations, and include the costs related to this new function in our research and development expenses. We expect that the consolidation will result in overall efficiencies and related cost savings.

For the years ended December 31, 2005 and 2004, our research and development expenses by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$ 69,536	$ 105,168
Ibis Division	12,931	13,306
Total research and development expenses	$ 82,467	$ 118,474

Drug Discovery & Development

Antisense Drug Discovery

Finding and testing novel chemistries, using these proprietary oligonucleotide chemistries in identifying 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. We have created inhibitors to thousands of genes, validated many targets and dissected numerous disease pathways. Additionally, we have created libraries of antisense inhibitors to identify novel gene function. Our advances in these areas have enhanced our own antisense drug discovery efforts and our patent portfolio through collaborations and intellectual property licenses while generating near-term revenue for us. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology. Through the efforts of our scientists in the antisense drug discovery group, we have produced second generation antisense drugs that have been shown to have increased potency, increased stability, an improved side effect profile and the potential for oral administration. With more than a decade focused on learning the capabilities of antisense technology and how these compounds behave in the body, our scientists have learned the organs and tissues in humans to which antisense therapy is effectively directed. Using this knowledge, we have strategically focused our research programs on those sites in the body that accept antisense readily, like the liver, kidney, fat tissue and bone marrow. These targets expand the current therapeutic scope of antisense research into new disease categories, including obesity, asthma, cardiovascular and neurodegenerative disease. The work of our scientists has given us the opportunity to enter into important drug discovery relationships with industry leaders like Lilly and Pfizer.

As we have advanced our antisense technology to a point where we and our partners now have extensive clinical and preclinical development pipelines that are full of product opportunities, we have far more drug assets than we can afford to develop on our own. As a result, we have significantly reduced our antisense drug discovery activities so that we can focus on our drugs in development, and we would expect to see our expenses for antisense drug discovery decrease further in 2006. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug discovery costs for the year ended December 31, 2005 were $17.9 million, compared to $38.4 million for the same period in 2004. The decrease of $20.5 million from 2004 to 2005 was principally the result of cost savings achieved as a result of our restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. In addition, under our Lilly collaboration extension,

we are no longer reimbursing Lilly for the cost of their scientists who are supporting the joint collaboration.

Antisense Drug Development

Our development activities reflect our efforts to advance our drugs through the various stages of preclinical, or animal studies, and human clinical trials. The development plans for our drugs are subject to numerous uncertainties like obtaining regulatory approval, market availability and successfully obtaining funding, which affects our research and development expenditures and capital resources. Prior to starting clinical trials, we test our potential products in numerous preclinical studies to identify disease indications for which they may be candidates. Once we have established that a preclinical drug has met certain clinical requirements and we have filed an Investigational New Drug Application, or IND, with the FDA, we may initiate clinical trials in the United States for that drug. It may take several years to complete clinical trials, with the length varying substantially according to the complexity, novelty and intended use of the product candidate. The following timelines represent our estimate of typical completion times for clinical trials we generally conduct: Phase 1—one year, Phase 2—one to two years, and Phase 3—two to four years. However, a number of factors including the required minimum number of patients, the ability to enroll suitable patients, the dosing regimens and the requisite follow-up periods, the clinical endpoints and inputs from our corporate partner, tend to vary from product to product and can impact the timing and magnitude of what we spend on each product in a particular period. These factors are outside our control and often result in dramatic fluctuations in the costs associated with each product on a period to period basis. As a result, we are unable to estimate the costs to complete our projects.

We may conduct multiple clinical trials on a drug, 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 drugs in certain indications in order to focus our resources on more promising drugs or indications. For example, in early 2005, we decided not to initiate additional studies of ISIS 14803 and ISIS 104838. Generally, Phase 3 clinical trials are the longest, largest and most expensive component of the drug development process. Further, products in Phase 3 trials represent the most near term possibility of commercial success. In addition, because Phase 3 trials typically involve a well-defined protocol and require dedicated resources, it is easier for us to separately capture costs associated with these projects. Our Phase 1 and Phase 2 programs are really 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, seven of our 13 drugs, which substantially reduce our development costs.

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

	December 31, 2005	December 31, 2004
Alicaforsen for Crohn’s disease	$ 417	$ 5,523
Other antisense development products	22,430	30,202
Development overhead costs	3,475	6,704
Total antisense drug development	$ 26,322	$ 42,429

Total antisense drug development expenditures were $26.3 million and $42.4 million for the years ended December 31, 2005 and 2004, respectively. The significant decrease of $16.1 million from 2004 to 2005 was primarily due to a decrease in costs associated with development activities for our first generation drugs, including alicaforsen for Crohn’s disease and ulcerative colitis. In addition, we realized cost savings due to our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012 and ISIS 113715, and the resulting decision to discontinue development of ISIS 104838 and ISIS 14803. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials.

We incurred development expenditures related to alicaforsen for Crohn’s disease of $417,000 and $5.5 million for the years ended December 31, 2005 and 2004, respectively. The decrease of $5.1 million was primarily due to the completion of our Phase 3 trials in December 2004. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with Crohn’s disease. In these trials, alicaforsen did not demonstrate statistically significant induction of clinical remission compared to placebo. As a result of these data, we decided not to invest further in the development of alicaforsen for Crohn’s disease. The 2005 expenses represent costs associated with closing out the program.

We incurred expenses related to our other products in development of $22.4 million and $30.2 million for the years ended December 31, 2005 and 2004, respectively. The decrease of $7.8 million was primarily the result of a decrease in development activity related to alicaforsen for ulcerative colitis and the discontinuation of ISIS 104838 and ISIS 14803. In December 2004, we announced the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen enema produced significant and long-lasting disease improvement. Costs for alicaforsen for ulcerative colitis have decreased in 2005 as compared to 2004 because we are using primarily internal resources as we prepare Phase 3 development plans for the drug. The decrease was offset in part by increased expenditures related to our most promising second generation drugs, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the lowering of high cholesterol. We recently initiated our Phase 2 program for ISIS 301012, including multiple studies for the treatment of high cholesterol and familial hypercholesterolemia.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. These costs for the year ended December 31, 2005 were $6.5 million. As discussed above, manufacturing and operations is a new function that was created in 2005 to provide manufacturing efficiencies and related cost savings. 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. We believe that it would be impractical to obtain comparative information for prior periods for this new function, and that such comparisons between any period in 2004 would be meaningless; therefore, we do not discuss these comparisons.

Ibis Division

Our Ibis research and development expenses are the result of our performance under our contracts with DARPA, the FBI, the CDC, the DHS and the NIAID, a part of the NIH, in support of the ongoing development of our TIGER biosensor system. We include in the expenses for our Ibis division all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our TIGER biosensor system. In addition, we allocate a portion of R&D support costs and general and administrative costs to our Ibis division.

Our Ibis division's research and development expenses for the years ended December 31, 2005 and 2004 were $12.9 million and $13.3 million, respectively. During 2004, Ibis purchased equipment at a cost of $3.2 million to build multiple TIGER biosensor systems. Because Ibis was assembling the systems in 2005 for which it had purchased equipment in 2004, Ibis' equipment purchases during 2005 of $1.2 million were significantly lower than in 2004. The decrease in equipment costs from 2004 to 2005, offset in part by increased costs for personnel and consultants to support the move toward commercialization, were the primary reasons for the decrease in Ibis' research and development expenses from 2004 to 2005. Ibis delivered its first two TIGER biosensor systems in 2005, and plans to deliver additional systems to its government partners in 2006. We expect our costs for our Ibis division to increase as we continue to expand this business.

R&D Support

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

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

	December 31,	
	2005	2004
Personnel costs	$ 5,739	$ 10,450
Occupancy	6,931	6,409
Depreciation and amortization	5,696	6,946
Insurance	1,123	1,179
Other	2,055	2,694
Total R&D support costs	$ 21,544	$ 27,678

R&D support costs for the years ended December 31, 2005 and 2004 were $21.5 million and $27.7 million, respectively. The decrease in 2005 was primarily due to decreased personnel, facilities, equipment depreciation and patent amortization costs resulting from our restructuring activities, which included employee terminations, consolidation and closure of facilities, and the write-down of equipment and patents. In 2005 and 2004, we allocated $2.8 million and $3.3 million of our R&D support costs to our Ibis division.

For the years ended December 31, 2005 and December 31, 2004, our R&D support costs by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$ 18,771	$ 24,374
Ibis Division	2,773	3,304
Total R&D support costs	$ 21,544	$ 27,678

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 and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

General and administrative expenses for the year ended December 31, 2005 totaled $8.4 million compared to $9.6 million for 2004. The decrease of $1.2 million from 2004 to 2005 was primarily related to a reduction in personnel and outside services costs resulting from our restructuring activities. We allocated $1.1 million and $924,000 of our general and administrative costs to Ibis in 2005 and 2004, respectively.

For the years ended December 31, 2005 and December 31, 2004, our general and administrative expenses by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$ 7,342	$ 8,658
Ibis Division	1,090	924
Total general and administrative expenses	$ 8,432	$ 9,582

Compensation Related to Stock Options

Compensation benefit for the year ended December 31, 2005 was $544,000, compared to compensation benefit of $6,000 for the year ended December 31, 2004. The changes in compensation benefit were primarily related to the effects of using variable accounting to account for stock options

associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with Accounting Principles Board, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44. APB 25 and FIN 44 require us to account for these exchanged options as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. We also recorded nominal expense in 2005 and 2004 related to stock options granted in prior years to consultants, and we accounted for these options in accordance with Emerging Issues Task Force Abstract No. 96-18, or EITF 96-18.

Restructuring Activities

During the fourth quarter of 2004, we recorded a $32.4 million charge for restructuring activities resulting from our strategic decision to reorganize and focus our resources on key programs. The 2004 charge for restructuring activities consisted of non-cash write-downs of tangible and intangible assets that we considered to be non-essential to our new focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. For the year ended December 31, 2005, we recorded $7.0 million in

costs associated with our restructuring activities. The 2005 charge for restructuring activities consisted of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore. In connection with the consolidation of our U.S. facilities, we sold three of our buildings during 2005. After deducting commissions, other expenses and the repayment of approximately $5.8 million of debt, we received net proceeds of approximately $7.9 million for the sales of the properties. We included a net gain of $1.5 million on the sales of these buildings in restructuring activities in 2005.

Investment Income

Investment income for the years ended December 31, 2005 and 2004 was $5.1 million and $3.0 million, respectively. The increase in interest income in 2005 over 2004 was primarily due to a gain of $951,000 realized on the sale of a portion of the equity securities of Alnylam that we owned and $2.0 million of non-cash income recorded in connection with the revaluation of warrants issued in connection with our August 2005 private placement. Prior to the registration statement for this private placement becoming effective, the potential existed for us to pay liquidated damages if such effectiveness did not occur. As a result, we allocated a portion of the offering proceeds to the warrants based on the warrants' fair value. We periodically revalued the warrants as a derivative instrument with the change in value recorded as interest income. In the fourth quarter of 2005, the registration statement became effective. As a result, the potential for liquidated damages lapsed resulting in interest income when the warrants were revalued. These increases were offset in part by lower average cash and investments balances in 2005 than in 2004.

Interest Expense

Interest expense for the year ended December 31, 2005 was $20.3 million, compared to $22.6 million for the same period in 2004. The $2.3 million decrease from 2004 to 2005 was primarily due to the effect of a lower debt balance during 2005 than during 2004 resulting from the conversion of our $100.0 million Lilly loan and a decrease from 2004 to 2005 in the carrying value of our term loan from Silicon Valley Bank. The effect of a lower debt balance in 2005 compared to 2004 was offset in part by the effect of a higher average interest rate in 2005 than in 2004 on our Silicon Valley Bank loan. The Silicon Valley Bank loan bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 7.00% at December 31, 2005, compared to 5.25% at December 31, 2004. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. In 2005, $10.8 million, compared to $13.0 million in 2004, of interest expense did not require cash payment. The amounts represent the accrual of interest expense related to our $100.0 million Lilly loan.

As a result of the Lilly loan conversion, we substantially reduced our debt obligations in 2005. Accordingly, we expect our interest expense to decrease in 2006.

Net Loss Applicable to Common Stock

For the years ended December 31, 2005 and 2004, we reported a net loss of $72.4 million and $142.5 million, respectively. Our net loss applicable to common stock was $72.4 million for the year ended December 31, 2005 and $142.9 million for 2004, including $361,000 of accreted dividends on preferred stock in 2004. There were no accreted dividends on preferred stock in 2005. The decrease in accreted dividends in 2005 from 2004 was the result of our agreement in June 2004 with a subsidiary of Elan to acquire Elan's minority interest in Orasense and HepaSense. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend. The decrease in the net loss applicable to common stock in 2005 from 2004 was primarily the result of a substantial decrease in operating expenses offset by a decrease in revenue, an increase in interest income,

and a decrease in interest expense as described previously. In addition, during 2005 and 2004, we incurred charges of $7.0 million and $32.4 million, respectively, related to restructuring activities. In 2005, we did not incur losses on investments. In 2004, we incurred a non-cash loss of $5.1 million principally related to the impairment of our equity investment in Alnylam. Alnylam's stock is currently trading significantly above its 2004 levels, which Isis believes reflects Alnylam's leading position in the field of RNAi.

Net Operating Loss Carryforward

At December 31, 2005, we had federal, foreign and California tax net operating loss carryforwards of approximately $510.5 million, $1.0 million, and $120.0 million, respectively. We also had federal and California research credit carryforwards of approximately $25.0 million and $17.5 million, respectively. The net operating losses, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal tax loss carryforwards and our research credit carryforwards will begin expiring in 2007 and 2006, 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 California tax loss carryforwards will begin expiring in 2005, unless utilized. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Years Ended December 31, 2004 and December 31, 2003

Revenue

Total revenue for the year ended December 31, 2004 was $42.6 million, compared to $50.0 million for the same period in 2003. The decrease in revenue of $7.4 million in 2004 primarily reflects the completion of our Phase 3 clinical trial of Affinitak in 2003, with an associated reduction in revenue for 2004, offset in part by increased revenue from our alliances and licenses, particularly with government agencies relating to our TIGER program, Alnylam, Eyetech, and Lilly. Our revenue fluctuates from period to period based on the timing of license fees and milestone payments earned, and other deliverables under agreements with our partners. For example, our fourth quarter 2004 revenue increased over the same period in 2003 primarily as a result of the $3.0 million milestone from Eyetech associated with Macugen's marketing clearance from the FDA.

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

	December 31	
	2004	2003
Drug Discovery and Development:		
Research and development revenue	$ 21,684	$ 40,605
Licensing and royalty revenue	10,007	523
	$ 31,691	$ 41,128
Ibis Division:		
Research and development revenue	$ 10,933	$ 8,862
Licensing and royalty revenue	—	—
	$ 10,933	$ 8,862
Total revenue:		
Research and development revenue	$ 32,617	$ 49,467
Licensing and royalty revenue	10,007	523
	$42,624	$49,900

Research and Development Revenue under Collaborative Agreements

Our revenue under the category research and development revenue under collaborative agreements for the year ended December 31, 2004, was $32.6 million, compared to $49.5 million for the year ended December 31, 2003. The decrease of $16.9 million in 2004 reflects the completion of our Phase 3 clinical trial of Affinitak in 2003 and an associated reduction in revenue for 2004, offset in part by increased revenue from our TIGER program, our strategic alliance with Alnylam and our research collaboration with Lilly, which included $1.5 million in revenue earned from Lilly in 2004 for the initiation of a Phase 1 clinical trial of LY2181308 and $750,000 in revenue earned from Lilly in 2004 for the license of LY2275796, a second generation antisense anti-cancer drug for clinical development.

Our Ibis division generates revenue from grants and contracts from United States government agencies, including DARPA, the CDC, the FBI, and the NIAID, a part of the NIH. During 2004, we received grants and contracts for up to $29.5 million in funding from various governmental agencies to further the development of our TIGER program. Our Ibis division generated revenue of $2.0 million and $10.9 million for the quarter and year ended December 31, 2004, respectively, including revenue related to equipment purchased on behalf of the respective government agencies. Also, we have approval to invoice our government partners an additional $8.6 million under our existing contracts and grants. We may receive continued approval to invoice our government partners under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of additional contract options by the contracting agencies. In addition, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards. We receive our DARPA funding through a subcontract with San Diego-based SAIC. This collaboration accounted for approximately 18% and 16% of our total revenue in 2004 and 2003, respectively.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $10.0 million for the year ended December 31, 2004, compared with $523,000 in 2003. The increase of $9.5 million primarily reflects $5.5 million we earned under our strategic alliance with Alnylam, and $4.0 million in milestones earned from Eyetech associated with Eyetech's filing of an NDA with the FDA for Macugen and the marketing clearance of Macugen by the FDA. In January 2005, we sold a portion of our royalty rights in Macugen to DRC, in exchange for aggregate payments of $24.0 million over the next three years.

Operating Expenses

Total operating expenses were $160.5 million and $129.0 million for the years ended December 31, 2004 and 2003, respectively. The increase of $31.5 million was primarily due to non-cash charges of $32.4 million for restructuring activities related to our strategic decision to reorganize and refocus our resources to advance our most promising second generation drugs and to develop our antisense technology. The 2003 operating expenses included a charge for restructuring activities of $1.8 million. The increase in 2004 was partially offset by the completion of our development activities for Affinitak, and changes to non-cash compensation due to variable accounting for stock options and in research and development and general and administrative expenses as we describe in the following paragraphs.

Total operating expenses for the year ended December 31, 2004 included a non-cash compensation benefit of approximately $6,000 due to variable accounting for stock options, compared to a non-cash compensation expense of $913,000 for 2003. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation related to stock options as a result of the variability in the company's stock price.

Research and Development Expenses

For the year ended December 31, 2004, our reported total research and development expenses were $118.5 million, compared to $117.0 million in 2003. Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis division and related R&D support costs. The increase of $1.5 million in 2004, compared to 2003, was primarily due to increased spending to support our TIGER program, start-up costs related to our Singapore laboratory, increased spending to support the completion of a large Phase 2 clinical program for alicaforsen enema in patients with ulcerative colitis, and increased spending to support our highest priority second generation drugs, ISIS 113715 and ISIS 301012. These increases were partially offset by the absence of expenses in 2004 related to Affinitak, which we stopped investing in during 2003, and the completion of our development activities for alicaforsen for Crohn's disease, ISIS 14803 and ISIS 104838.

For the year ended December 31, 2004, our research and development expenses by segment were as follows (in thousands):

	December 31, 2004
Drug Discovery and Development	$ 105,168
Ibis Division	13,306
Total research and development expenses	$ 118,474

Antisense Drug Discovery

Antisense drug discovery costs included in research and development expenses for the year ended December 31, 2004 totaled $38.4 million, compared to $37.3 million for 2003. The increase of $1.1 million in 2004 over 2003 was principally the result of start-up costs related to our Singapore laboratory.

Antisense Drug Development

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

	December 31,	
	2004	2003
Affinitak	$ —	$ 5,072
Alicaforsen for Crohn's disease	5,523	6,519
Other antisense development products	30,202	29,323
Development overhead costs	6,704	4,234
Total antisense drug development	$ 42,429	$ 45,148

Antisense drug development costs included in research and development expenses totaled $42.4 million and $45.1 million for the years ended December 31, 2004 and 2003, respectively. The decrease of $2.7 million in 2004 was primarily due to the completion in 2003 of our Phase 3 trial of Affinitak and the completion in 2004 of our development activities for alicaforsen for Crohn's disease, offset in part by increased clinical development expenses for other products in development.

There were no expenditures related to Affinitak in 2004. Expenditures related to Affinitak in 2003 were $5.1 million. The decrease was primarily due to a reduction in costs associated with the development of Affinitak following the disappointing results from the first Phase 3 trial of Affinitak and the decision not to file an NDA in 2003. In October 2004, we and Lilly reported the results of a second Phase 3 clinical trial of Affinitak in combination with Gemzar and cisplatin in patients with NSCLC. Findings from this trial, which was sponsored by Lilly, were similar to the results of the first Isis-sponsored Phase 3 study of Affinitak for NSCLC. As a result of these data, we decided not to invest further in the development of Affinitak.

Development expenditures related to alicaforsen for Crohn's disease totaled $5.5 million and $6.5 million for the years ended December 31, 2004 and 2003, respectively. The decrease of $1.0 million in 2004 was primarily due to the completion of our Phase 3 trials in December 2004.

We incurred expenses related to our other products in development of $30.2 million and $29.3 million for the years ended December 31, 2004 and 2003, respectively. The increase of $900,000 was primarily the result of an increase in development activity related to Phase 1 and Phase 2 trials for our ulcerative colitis, diabetes, cancer and cardiovascular drugs, as well as expenses related to other products in the early stages of development.

Ibis Division

Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our TIGER program.

Our Ibis division's research and development expenditures for the year ended December 31, 2004 totaled $10.0 million, compared to $9.3 million for the year ended December 31, 2003. The increase of $700,000 in 2004 was the result of our performance under our contracts with DARPA, the FBI, the NIAID, a part of the NIH, and the CDC, in support of our ongoing development of our TIGER program. We include in our Ibis division expenses all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. We began reporting our Ibis division as a separate operating segment in 2004. Accordingly, we allocate a portion of R&D support and general and administrative costs to this segment. In 2004, we allocated approximately $4.2 million of costs related to

R&D support and general and administrative to Ibis. Prior to 2004, we did not allocate R&D support or general and administrative costs to our separate operating segments. We believe that it would be impractical to obtain comparative information for prior periods, and that such comparisons between any period in 2004 and the comparable periods in prior years for R&D support costs and general and administrative expenses by segment would be meaningless; therefore, we do not discuss these comparisons below. We expect our costs for our Ibis division to increase as we continue to expand this business.

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. Generally these costs represent approximately 17% to 23% of our total annual research and development expense.

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

	December 31,	
	2004	2003
Personnel costs	$ 10,450	$ 9,844
Occupancy	6,409	6,734
Depreciation and amortization	6,946	5,710
Insurance	1,179	1,132
Other	2,694	1,760
Total R&D support costs	$ 27,678	$ 25,180

R&D support costs for the year ended December 31, 2004 totaled $27.7 million, compared to $25.2 million for the year ended December 31, 2003. The increase of $2.5 million in 2004 was primarily due to increased personnel, facilities and equipment depreciation and patent amortization costs, which are all costs that support the entire research and development organization. We allocated $3.3 million of our 2004 R&D support costs to our Ibis division as a result of reporting Ibis as a separate segment beginning in 2004. Prior to 2004, we did not allocate R&D support costs to our separate operating segments. We believe that it would be impractical to obtain comparative information for prior periods, and that such comparisons between any period in 2004 and the comparable periods in prior years for R&D support costs by segment would be meaningless; therefore, we do not discuss these comparisons.

For the year ended December 31, 2004, our R&D support costs by segment were as follows (in thousands):

	December 31, 2004
Drug Discovery and Development	$ 24,374
Ibis Division	3,304
Total R&D support costs	$ 27,678

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 and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

General and administrative expenses for the year ended December 31, 2004 totaled $9.6 million compared to $9.3 million for the year ended December 31, 2003. The increase of $300,000 in 2004 was primarily related to our Sarbanes-Oxley Act Section 404 implementation activities. We allocated $924,000 of our 2004 general and administrative costs to our Ibis division as a result of reporting Ibis as a separate segment beginning in 2004. Prior to 2004, we did not allocate general and administrative costs to our separate operating segments. We believe that it would be impractical to obtain comparative information for prior periods, and that such comparisons between any period in 2004 and the comparable periods in prior years for general and administrative costs by segment would be meaningless; therefore, we do not discuss these comparisons.

For the year ended December 31, 2004, our general and administrative expenses by segment were as follows (in thousands):

	December 31, 2004
Drug Discovery and Development	$ 8,658
Ibis Division	924
Total general and administrative expenses	$ 9,582

Compensation Related to Stock Options

Compensation benefit for the year ended December 31, 2004 was $6,000, compared to compensation expense of $913,000 for the year ended December 31, 2003. The changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with Accounting Principles Board, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44. APB 25 and FIN 44 require us to account for these exchanged options as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. We also recorded nominal expense in 2004 related to stock options granted in prior years to consultants, and we accounted for these options in accordance with Emerging Issues Task Force Abstract No. 96-18, or EITF 96-18.

Restructuring Activities

During the fourth quarter of 2004, we recorded a $32.4 million charge for restructuring activities resulting from our strategic decision to reorganize and refocus our resources to advance our most promising second generation drugs and to continue our development of antisense technology. The 2004 charge for

restructuring activities consists of non-cash write-downs of tangible and intangible assets that are non-essential to our current focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. The 2003 operating expenses included a $1.8 million charge for restructuring activities.

Investment Income

Investment income for the years ended December 31, 2004 and 2003 was $3.0 million and $5.1 million, respectively. The $2.1 million decrease in investment income in 2004 compared to 2003 was primarily due to our lower average cash balance in 2004 compared to 2003.

Interest Expense

Interest expense for the year ended December 31, 2004 was $22.6 million, compared to $18.7 million for the same period in 2003. The $3.9 million increase in interest expense in 2004 compared to 2003 was

primarily due to the effect of a higher debt balance during 2004 than during 2003 related to an increase in the loan to fund our Lilly research collaboration, offset by a decrease in the carrying value of our term loan from Silicon Valley Bank. A decrease in the average interest rate on our debt offset, in part, the effect of a higher average debt balance. The decrease in the average debt interest rate was primarily due to the retirement, in the fourth quarter of 2003, of higher interest rate debt with proceeds from our $32.0 million term loan from Silicon Valley Bank secured in December 2003. The debt we retired in the fourth quarter of 2003 consisted of convertible partner debt that carried interest rates ranging from 8.5% to 12%. The Silicon Valley Bank term loan bears interest at the prime rate, which was 5.25% at December 31, 2004. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. In 2004, $13.0 million of the $22.6 million in interest expense did not require cash payment. This represents the accrual of interest expense related to the $100.0 million loan Lilly has made available to us to fund the research collaboration.

Net Loss Applicable to Common Stock

For the years ended December 31, 2004 and 2003, we reported a net loss of $142.5 million and $95.0 million, respectively. Our net loss applicable to common stock was $142.9 million for the year ended December 31, 2004, and $95.7 million for the year ended December 31, 2003, including $361,000 and $694,000, respectively, of accreted dividends on preferred stock. The decrease in accreted dividends in 2004 from 2003 was the result of our agreement in June 2004 with a subsidiary of Elan to acquire Elan's minority interest in Orasense and HepaSense. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend. The increase in the net loss applicable to common stock in 2004 from 2003 was primarily the result of a decrease in revenue, increase in operating expenses, decrease in interest income, and increase in interest expense as described previously. In addition, during 2004 and 2003, we incurred charges of $32.4 million and $1.8 million, respectively, related to restructuring activities. In 2003, we incurred a non-cash loss on investments of $2.4 million related to the impairment of our investments in ATL and Hybridon. In 2004, we incurred a non-cash loss on investments of $5.1 million principally related to the impairment of our equity investment in Alnylam, reflecting the decrease in the market value of Alnylam's stock in 2004, which we believe was primarily a result of financial market conditions related to biotechnology companies. Our Alnylam alliance, established in 2004 to develop RNAi drugs, provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery.

Net Operating Loss Carryforward

At December 31, 2004, we had federal, foreign and California tax net operating loss carryforwards of approximately $517.1 million, $530,000 and $140.4 million, respectively. We also had federal and California research credit carryforwards of approximately $23.5 million and $10.0 million, respectively. The net operating losses, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal tax loss carryforwards and our research credit carryforwards will begin expiring in 2007 and 2005, 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 California tax loss carryforwards will begin expiring in 2006, unless utilized. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit

carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. 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, 2005, we have earned approximately $483.2 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $642.4 million from the sale of equity securities. We have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2005, we had cash, cash equivalents and short-term investments of $94.4 million, working capital of $82.1 million and stockholders' equity of $2.7 million. In comparison, we had cash, cash equivalents and short-term investments of $103.9 million, working capital of $82.2 million and stockholders' deficit of $72.1 million as of December 31, 2004. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, including our restructuring activities, pursue patents, and to pay our debt and capital lease obligations offset principally by the $48.2 million of net proceeds we received from the private placement offering in August 2005 of 12 million shares of our common stock.

As of December 31, 2005, our debt and other obligations totaled $147.8 million, compared to $258.9 million at December 31, 2004. The decrease in our debt and other obligations was primarily due to the conversion into common stock of our $100.0 million Lilly loan, and to a lesser extent, the declining balance on our Silicon Valley Bank term loan and the repayment of a mortgage loan secured by properties that we sold.

We will continue to use lease financing as long as the terms remain commercially attractive. Consistent with this, in July 2005, we entered into a $3.0 million equipment lease line with General Electric Capital Corporation. The lease line is effective for purchases through May 2006 and carries an interest rate of the three-year treasury rate plus 1.06% at the time of drawdown. This lease line will be secured by any equipment purchased under the line. To date, we have not drawn any funds under this lease line.

Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements at least through 2007.

The following table summarizes our contractual obligations as of December 31, 2005. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
			(in millions)		
5½% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ 125.0	$ —
Standard Operating Debt	$ 20.2	$ 6.3	$ 13.9	$ —	$ —
Capital Lease and Other Obligations	$ 2.6	$ 1.6	$ 1.0	$ —	$ —
Operating Leases	$ 21.4	$ 3.4	$ 4.2	$ 2.9	$ 10.9

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a term loan from Silicon Valley Bank. During 2005, we repaid in full a mortgage loan of $5.8 million when we sold the real properties that secured the loan.

In August 2005, we converted our $100.0 million Lilly loan into 2.5 million shares of our common stock. Under the terms of the conversion and Lilly collaboration extension, Lilly agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration doesn't terminate earlier, in exchange for certain credits against milestone payments and royalties in the event of a stock price decline. The impact to the balance sheet of the loan conversion was reflected in our financial results as a reduction in long term debt and an increase in shareholders' equity.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 7.00% at December 31, 2005. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. We used the proceeds from the loan to pay off existing debt to Elan of $5.1 million plus accrued interest and to BI of $22.6 million plus accrued interest. The carrying value of the term loan at December 31, 2005 and 2004 was $20.2 million and $26.1 million, respectively.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At December 31, 2005 and 2004, the principal outstanding on the notes was $125.0 million.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2005 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

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

Item 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a)(1) and (2), and incorporated 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 2005 with our Independent Auditors.

Item 9A. Controls and Procedures

Evaluation of 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, 2005 to ensure that information required to be disclosed by us in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms.

Changes in Internal Controls

That 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, 2005, 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, 2005.

Our management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2005 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 on Internal Controls Over Financial Reporting

To the Stockholders and the
Board of Directors of Isis Pharmaceuticals, Inc.

We have audited management's assessment, included in the accompanying Management's Report on Internal Control over Financial Reporting, that Isis Pharmaceuticals, Inc. (the "Company") maintained effective internal control over financial reporting as of December 31, 2005, based on criteria established in

Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the "COSO criteria"). The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment about the effectiveness of internal control over financial reporting. Our responsibility is to express an opinion on management's assessment and an opinion on the effectiveness of the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, evaluating management's assessment, testing and evaluating the design and operating effectiveness of internal control, 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, management's assessment that the Company maintained effective internal control over financial reporting as of December 31, 2005, is fairly stated, in all material respects, based on the COSO criteria. Also, in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2005, based on the COSO criteria.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of the Company as of December 31, 2005 and 2004 and the related consolidated statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2005, and our report dated March 7, 2006 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 7, 2006

Item 9B. Other Information

Not applicable

Item 9B. Other Information

Not applicable

PART III

Item 10. Directors and Executive Officers of the Registrant

We incorporate by reference the information required by this Item with respect to Directors and Audit Committee financial expert by reference from the information under the caption "Election of Directors" and "Audit Committee", respectively, contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about March 22, 2006 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2006 Annual Meeting of Stockholders to be held on May 3, 2006.

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

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption "Executive Compensation" and "Compensation Committee Interlock and Insider Participation" 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" and "Equity Compensation Plan Information" 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, 2005.

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)	4,392,000	$ 7.88	4,304,000 (c)
Equity compensation plans not approved by stockholders(b)	3,588,000	$ 7.84	1,976,000
Total	7,980,000	$ 7.86	6,280,000

(a) Consists of three Isis plans: 1989 Stock Option Plan, 2002 Non-Employee Directors' Stock Option Plan and the 2000 Employee Stock Purchase Plan.

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

(c) Of these shares, 50,944 remained available for purchase under the 2000 Employee Stock Purchase Plan as of December 31, 2005. The 2000 Employee Stock Purchase Plan incorporates an evergreen formula pursuant to which on each January 1 for the first 9 anniversaries, we automatically increase the aggregate number of shares reserved for issuance under the plan by the lesser of (i) 1% of the total number of shares of common stock outstanding on such anniversary date or (ii) 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, 2005, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 3,588,000 shares have been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 426,000 shares have been exercised under the 2000 Plan, and 1,976,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the optionee's employment or service as a consultant or term as an affiliate. Options granted pursuant to the April 2003 stock option exchange program as discussed in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," and in the Notes to Consolidated Financial

Statements, expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the optionee's employment or service as a consultant or term as an affiliate. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

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

In the event of:

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

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

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. In addition, as of December 31, 2005, approximately 3,588,000 stock awards granted under the 2000 plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

Item 13. Certain Relationships and Related Transactions

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 on pages 72 through 77.

(b) Exhibits

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

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 16th day of March, 2006.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANELY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.

Chairman of the Board, President and Chief Executive Officer (Principal executive officer)

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	March 16, 2006
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 16, 2006
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 16, 2006
/s/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	March 16, 2006
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 16, 2006
/s/ JOSEPH KLEIN Joseph Klein, III.	Director	March 16, 2006
/s/ FREDERICK T. MUTO Frederick T. Muto	Director	March 16, 2006
/s/ JOHN C. REED, M.D. Ph.D. John C. Reed, M.D., Ph.D.	Director	March 16, 2006
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 16, 2006

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 April 9, 2001.(19)
3.3	Bylaws.(19)
4.3	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	Specimen Common Stock Certificate.(1)
4.5	Form of Right Certificate.(17)
4.6	Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement,

		Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(14)
4.7		Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.8		Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.9		Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(16)
4.10		Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 5 1/2% Convertible Subordinated Notes due 2009.(16)
4.11		Form of 5 1/2% Convertible Subordinated Note due 2009.(16)
4.12		Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(37)
4.13		Form of Warrant expiring August 23, 2005.(37)
10.1		Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2	*	Registrants 1989 Stock Option Plan, as amended.(2)
10.3	*	Registrants 1992 Non-Employee Directors Stock Option Plan, as amended.(4)
10.4	*	Registrants Employee Stock Purchase Plan.(10)
10.5		Form of Employee Assignment of Patent Rights.(1)
10.6	*	Registrants 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.11		Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.13		Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)

10.14		Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.15		Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.17		Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.18		Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.19		Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.20		Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.21		Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.22		Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc.(22)
10.23		Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted). (24)
10.24		Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted). (24)
10.26		License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.31		Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.32		Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.35		Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(38)
10.36		Registrant's 2002 Non-Employee Directors' Stock Option Plan.(31)
10.37		Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(31)
10.41	*	Form of Severance Agreement dated April 2003 entered into between the Registrant Stanley T. Crooke and B. Lynne Parshall.(32)

10.42 Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted).(33)

10.43* Amendment No. 1 to Isis Pharmaceuticals, Inc. 2000 Employee Stock Purchase Plan.(33)

10.44 Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement.(12)

10.47 Subcontract No. 44076514 dated February 26, 2004 between the Registrant and Science Applications International Corporation (with certain confidential information deleted).(13)

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

10.49 Investor Rights Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc.(23)

10.50 Securities Purchase Agreement dated June 4, 2004 between the Registrant and Elan Pharmaceutical Investments II, Ltd.(26)

10.51 Development Agreement dated September 30, 2004 between the Registrant and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted).(34)

10.52 Amendment No. 1 to License Agreement between the Registrant and Eyetech.(39)

10.53 Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(39)

10.54 Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(39)

10.55* Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(39)

10.56* Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(39)

10.57* Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(39)

10.58 Collaboration and License Agreement between the Registrant and Sarissa, Inc., dated Feb 10, 2005. (39)

10.59 Amendment No.1 to Rights Agreement dated April 7, 2005.(35)

10.60 Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted).(36)

10.61 Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(38)

10.62 Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(38)

10.63 Notice of Grant Award issued August 1, 2005 by the Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Disease (with certain confidential information deleted).(38)

10.64 Form of Subcontract Agreement between the Registrant and Science Applications International Corporation.(38)

10.65* Letter dated February 27, 2005 extending Dr. Crooke's severance benefit agreement.(39)

10.66* Letter dated February 27, 2005 extending Ms. Parshall's severance benefit agreement.(39)

14.1 Registrant's Code of Ethics and Business Conduct.(12)

21.1 List of Subsidiaries for the Registrant.

23.1 Consent of Independent Registered Public Accounting Firm.

24.1 Power of Attorney. Reference is made to page 57.

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

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

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

99.2 Form of Confidentiality Agreement.(11)

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

(2) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2004 Annual Meeting of Stockholders, filed with the SEC on April 12, 2004, and incorporated herein by reference.

(3) Not used.

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 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, 1998 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1998 and incorporated herein by reference.

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

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

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

(12) Filed as an exhibit to the Registrant's Annual Report Form 10-K for the year ended Dec 31, 2003 and incorporated herein by reference.

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

(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2000 and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.

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

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

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

(20) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

(21) Filed as an exhibit to the Registrant's Report on Form 8-K filed October 29, 2001 and incorporated herein by reference.

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

(23) Filed as Exhibit 10.25 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

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

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

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

(27) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2002 and incorporated herein by reference.

(28) Filed as an exhibit to the Registrant's Report on Form 8-K dated September 16, 2002 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, 2002 and incorporated herein by reference.

(30) Filed as an exhibit to the Registrant's Report on Form 8-K dated November 6, 2002 and incorporated herein by reference.

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

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

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

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

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

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

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

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

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

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

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

ISIS PHARMACEUTICALS, INC.

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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. and subsidiaries as of December 31, 2005 and 2004, and the related consolidated statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2005. 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. and subsidiaries at December 31, 2005 and 2004, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2005, in conformity with U.S. generally accepted accounting principles.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the effectiveness of Isis Pharmaceuticals, Inc.'s and subsidiaries' internal control over financial reporting as of December 31, 2005, based on the criteria established in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 7, 2006 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 7, 2006

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share data)

	December 31, 2005	December 31, 2004
ASSETS		
Current assets:		
Cash and cash equivalents	$ 3,650	$ 27,250
Short-term investments	90,739	76,633
Contracts receivable	3,918	10,048
Inventory	951	2,722
Other current assets	6,600	8,956
Total current assets	105,858	125,609
Property, plant and equipment, net	9,130	28,454
Licenses, net	23,770	26,104
Patents, net	18,773	19,097

Deposits and other assets	3,201	3,854
Investments in corporate securities	5,641	5,307
Total assets	$ 166,373	$ 208,425
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 2,095	$ 6,967
Accrued compensation	3,706	3,475
Accrued liabilities	8,643	8,238
Current portion of long-term obligations	7,835	10,546
Current portion of deferred contract revenue	1,514	14,190
Total current liabilities	23,793	43,416
5½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	14,915	111,611
Long-term deferred contract revenue, less current portion	—	531
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 100,000,000 shares authorized, 72,201,505 and 57,447,333 shares issued and outstanding at December 31, 2005 and 2004, respectively	72	57
Additional paid-in capital	770,263	623,706
Deferred compensation	—	(72)
Accumulated other comprehensive income	3,178	2,623
Accumulated deficit	(770,848)	(698,447)
Total stockholders' equity (deficit)	2,665	(72,133)
Total liabilities and stockholders' equity (deficit)	$ 166,373	$ 208,425

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

(In thousands, except for per share amounts)

	Years Ended December 31,		
	2005	2004	2003
Revenue:			
Research and development revenue under collaborative agreements	$ 28,610	$ 32,617	$ 49,467
Licensing and royalty revenue	11,523	10,007	523
Total revenue	40,133	42,624	49,990
Expenses:			
Research and development not including compensation (benefit) related to stock options of ($436), ($8), and $673 in 2005, 2004 and 2003, respectively	82,467	118,474	116,963
General and administrative not including compensation (benefit) related to stock options of ($108), $2, and $240 in 2005, 2004, and 2003, respectively	8,432	9,582	9,289
Compensation (benefit) related to stock options	(544)	(6)	913
Restructuring activities	6,960	32,427	1,803
Total operating expenses	97,315	160,477	128,968
Loss from operations:	(57,182)	(117,853)	(78,978)
Investment income	5,094	2,999	5,100
Interest expense	(20,313)	(22,592)	(18,680)
Loss on investment	—	(5,057)	(2,438)
Net loss	(72,401)	(142,503)	(94,996)
Accretion of dividends on preferred stock	—	(361)	(694)
Net loss applicable to common stock	$ (72,401)	$ (142,864)	$ (95,690)
Basic and diluted net loss per share	$ (1.15)	$ (2.52)	$ (1.73)
Shares used in computing basic and diluted net loss per share	62,877	56,642	55,463

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)

Years Ended December 31, 2005, 2004 and 2003

(In thousands)

Description	Preferred stock Shares	Preferred stock Amount	Preferred stock Dividend Accretion	Common stock Shares	Common stock Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2002	12	$ 12,015	$ 1,866	55,216	$ 55	$ 602,101	$ (59)	$ (608)	$ (459,893)	$ 155,477
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(95,690)	(95,690)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	4,084	—	4,084
Comprehensive loss	—	—	—	—	—	—	—	—	—	(91,606)
Dividends accrued on preferred stock	—	—	694	—	—	—	—	—	—	694
Deferred compensation	—	—	—	—	—	1,148	(1,148)	—	—	—
Options exercised and employee stock purchase plan	—	—	—	341	1	1,699	—	—	—	1,700
Compensation benefit relating to the granting of options							913			913
Balance at December 31, 2003	12	$ 12,015	$ 2,560	55,557	$ 56	$ 604,948	$ (294)	$ 3,476	$ (555,583)	$ 67,178
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(142,864)	(142,864)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(853)	—	(853)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(143,717)
Dividends accrued on preferred stock	—	—	361	—	—	—	—	—	—	361
Deferred compensation	—	—	—	—	—	(228)	228	—	—	—
Options exercised and employee stock purchase plan	—	—	—	834	—	4,051	—	—	—	4,051
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(6)	—	—	(6)
Conversion of preferred stock into common stock	(12)	(12,015)	(2,921)	1,056	1	14,935	—	—	—	—
Balance at December 31, 2004	—	$ —	$ —	57,447	$ 57	$ 623,706	$ (72)	$ 2,623	$ (698,447)	$ (72,133)
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	(72,401)	(72,401)	
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	555		555
Comprehensive loss	—	—	—	—	—	—	—	—	—	(71,846)
Deferred compensation	—	—	—	—	—	61	16	—	—	77
Options exercised and employee stock purchase plan	—	—	—	254	1	989	—	—	—	990
Compensation benefit relating to the granting of options	—	—	—	—	—	(678)	56	—	—	(622)
Conversion of Lilly debt	—	—	—	2,500	2	99,998	—	—	—	100,000
Private Placement Offering	—	—	—	12,000	12	46,187	—	—	—	46,199
Balance at December 31, 2005	—	$ —	$ —	72,201	$ 72	$ 770,263	$ —	$ 3,178	$ (770,848)	$ 2,665

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Years Ended December 31, 2005	2004	2003
Operating activities:			
Net loss	$ (72,401)	$ (142,503)	$ (94,996)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	5,817	8,401	8,551
Amortization of patents	1,545	1,442	1,217
Amortization of licenses	2,326	2,327	2,485
Compensation (benefit) related to stock options	(544)	(6)	913
Deferred interest on long-term debt	10,795	13,049	5,369
Loss on investments	—	5,057	2,438
Non-cash restructuring activities	—	32,427	—
Non-cash losses related to patents and fixed assets	3,087	2,275	2,813
Income from variable accounting of stock warrants	(1,980)	—	—
Gain on disposal of property, plant and equipment	(1,455)	—	—
Changes in operating assets and liabilities:			
Contracts receivable	5,380	(7,391)	12,249
Inventory	1,771	(9,699)	(2,905)
Other current and long-term assets	(7)	1,373	962
Accounts payable	(4,872)	3,247	(1,804)
Accrued compensation	231	(674)	819
Accrued liabilities	406	1,711	(267)
Deferred contract revenues	(11,840)	(12,787)	(33,318)
Net cash used in operating activities	(61,741)	(101,751)	(95,474)
Investing activities:			
Purchase of short-term investments	(64,103)	(72,479)	(152,910)
Proceeds from the sale of short-term investments	50,213	176,147	156,943
Purchases of property, plant and equipment	(422)	(3,526)	(7,554)
Proceeds from the sale of property, plant and equipment	14,020	—	—
Licenses and other assets	(2,451)	(6,411)	(6,404)
Strategic investments in corporate securities	—	(10,000)	—
Proceeds from the sale of strategic investments	3,283	—	—
Investments in affiliates	—	—	(5,193)
Net cash provided by (used in) investing activities	540	83,731	(15,118)
Financing activities:			
Net proceeds from issuance of equity	49,168	4,051	1,700
Proceeds from long-term borrowing	4,603	24,470	67,049
Principal payments on debt and capital lease obligations	(16,170)	(16,368)	(26,896)
Net cash provided by financing activities	37,601	12,153	41,853

Net decrease in cash and cash equivalents	(23,600)	(5,867)	(68,739)
Cash and cash equivalents at beginning of year	27,250	33,117	101,856
Cash and cash equivalents at end of year	$ 3,650	$ 27,250	$ 33,117
Supplemental disclosures of cash flow information:			
Interest paid	$ 8,877	$ 8,990	$ 12,778
Supplemental disclosures of non-cash investing and financing activities:			
Conversion of contract receivable into long-term investment	$ 750	$ —	$ —
Additions to long-term investments for acquired corporate securities	$ —	$ —	$ 750
Conversion of debt into common stock	$ 100,000	$ —	$ —
Conversion of preferred stock into common stock	$ —	$ 14,934	$ —
Decrease in inventory and deferred revenue	$ —	$ —	$ 8,750
Decrease in property, plant and equipment and notes payable	$ —	$ —	$ 21,200

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2005

1. Organization and Significant Accounting Policies

Basis of Presentation

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. (“the Company”) and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Limited, Hepasense, Ltd., and Orasense, Ltd. On July 25, 2005, Isis dissolved the Hepasense, Ltd. subsidiary. As more fully described in *Note 8—Restructuring Activities*, the Company closed its Singapore operations in early 2005.

Organization and business activity

Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, Isis Pharmaceuticals was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc. (“Isis” or the “Company”), in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share

Isis follows the provisions of Statement of Financial Accounting Standards (SFAS) No. 128 *Earnings per Share*. Isis computes basic loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period (“Basic EPS method”). Isis computes diluted earnings (loss) per common share using the weighted-average number of common and dilutive common equivalent shares outstanding during the period (“Diluted EPS method”). Diluted common equivalent shares of 13.0 million at December 31, 2005 consisted of shares issuable upon exercise of stock options and convertible debt. As Isis incurred a loss in the years ended December 31, 2005, 2004 and 2003, Isis 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 Isis records contract revenue as earned based on the performance requirements of Isis’ collaborative research and development contracts. Isis recognizes contract fees for which no further performance obligations exist when Isis receives the payments or when Isis is reasonably certain it can collect the receivable. Isis records payments received in excess of amounts earned as deferred contract revenue. The Company expenses research and development costs as incurred. For the years ended December 31, 2005, 2004 and 2003, research and development costs of approximately $30.4 million, $36.3 million, and $30.2 million, respectively, were related to collaborative research and development arrangements.

Revenue recognition

Isis recognizes revenue when all of its contractual obligations are satisfied and collection of the underlying receivable is reasonably assured.

ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2005

1. Organization and Significant Accounting Policies (Continued)

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone’s performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21 (“EITF 00-21”)

Accounting for Revenue Arrangements with Multiple Deliverables. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis recognizes revenue from federal contracts and grants in the period in which it pays for the related expenditures. Isis recognizes revenue from product sales as it ships the products. Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured.

As part of Isis' alliance with Eli Lilly and Company ("Lilly") in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. In August 2005, Isis converted the loan into 2.5 million shares of its common stock. During the four years prior to conversion Isis made quarterly draw downs on the loan, which Isis discounted to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this value as deferred revenue and recognized it as revenue over the period of performance. This is more fully described in *Note 4—Long-Term Obligations and Commitments and Note 6—Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, and if Isis is not required to provide services in the future.

1. Organization and Significant Accounting Policies (Continued)

Concentration of credit risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. Isis and its 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

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal period. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income. During 2005, Isis sold a portion of its investment in Alnylam Pharmaceuticals, Inc. resulting in a realized gain of $951,000. Further, Isis determined that there were no other-than-temporary declines in value of investments during the year. During the third quarter of 2004, Isis recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of the Company's equity investment in Alnylam. This loss on investments reflected a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. In the fourth quarter of 2004, Isis recorded a net unrealized gain of $1.4 million related to its equity investment in Alnylam as a separate component of stockholders' equity. This reflected the increase in the market value of the investment since the impairment in the third quarter of 2004. Additionally, Isis recorded a net unrealized gain of $2.8 million in 2005 reflecting the further increase in market value of its investment in Alnylam.

Inventory valuation

Isis includes in inventory 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. Isis expenses these costs when it delivers its drugs to partners, or as it provides these drugs for its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. Isis considers several factors in estimating the net realizable value; including shelf life of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. In 2004, Isis reduced the carrying value of its inventory by $21.0 million related to its restructuring activities. (Note 8—Restructuring Activities).

1. Organization and Significant Accounting Policies (Continued)

Inventory includes the following categories as of December 31, 2005 and 2004 (net realizable value, in thousands):

	December 31,	
Raw materials	$ 951	$ 1,329
Finished goods	—	1,393
	$ 951	$ 2,722

Property, plant and equipment

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

	December 31,	
	2005	2004
Land	$ —	$ 1,163
Buildings and improvements	10,752	30,305
Equipment and computer software	21,895	27,234
Furniture and fixtures	1,533	1,959
	34,180	60,661
Less accumulated depreciation	(25,050)	(32,207)
	$ 9,130	$ 28,454

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

Building	31.5 years
Building improvements	15 years
Manufacturing facilities	10 years
Equipment	5 years
Computer software	3 years
Furniture and fixtures	5 years

Leasehold improvements are depreciated using the shorter of the estimated useful life or remaining lease term.

Licenses

Isis obtains licenses from third parties and capitalizes the costs related to exclusive licenses. Isis' license from Hybridon comprises the majority of the license balance as of December 31, 2005, 2004 and 2003. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 8 years and 15 years. Accumulated amortization related to licenses was $12.2 million and $9.8 million at December 31, 2005 and 2004, respectively. Based on existing licenses,

1. Organization and Significant Accounting Policies (Continued)

estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2006, 2007, 2008, 2009 and 2010.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews its capitalized patent costs regularly to determine that they include costs for patent applications Isis is pursuing. Isis evaluates costs related to patents that the Company is not actively pursuing for impairment and writes off any of these costs, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued. The weighted average remaining life of issued patents was 5.2 years and 6.1 years at December 31, 2005 and 2004, respectively. In 2005 and 2004, Isis recorded a non-cash charge of $1.7 million and $6.1 million, respectively, related to the write-down of its patent costs to their estimated net realizable values (*Note 8—Restructuring Activities).*

Accumulated amortization related to patents was $7.0 million and $5.4 million at December 31, 2005 and 2004, respectively. Based on existing patents, estimated amortization expense related to patents is as follows (in millions):

Years Ending December 31,	Amortization (in millions)
2006	$1.5
2007	$1.4
2008	$1.3
2009	$1.2
2010	$1.0

Investment in affiliates

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. In June 2004, Isis acquired Elan's minority interest in Orasense and HepaSense. As a result, Isis owned 100% of Orasense and HepaSense at December 31, 2004. Isis dissolved the Hepasense subsidiary in July 2005. At December 31, 2005, Isis owned 100% of Orasense.

1. Organization and Significant Accounting Policies (Continued)

Fair value of financial instruments

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

Long-lived assets

Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may have been impaired. Isis has adopted SFAS 144, *Accounting for the Impairment of Long-Lived Assets*. In 2005 and 2004, Isis recorded a charge of $15.6 million and $11.5 million, respectively, related to the write-down of equipment and intangible assets to their estimated net realizable values. (*Note 8—Restructuring Activities).*

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.

Consolidation of variable interest entities

Isis has implemented the provisions of Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, 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, 2005, Isis had collaborative arrangements with three entities that it considers to be Variable Interest Entities ("VIE") under FIN 46.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible note. Isis expensed the payments when made. The note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1.0 million convertible note. The note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed iCO 007, an antisense drug to iCo in exchange for a $500,000 upfront fee consisting of a $250,000 cash payment and a $250,000 convertible note. The note will convert into securities that iCo issues in a

1. Organization and Significant Accounting Policies (Continued)

financing. Isis has recognized a valuation allowance of $250,000 to offset the note, as realization of this asset is uncertain. In December 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate iCo's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

Stock-based compensation

In January 2000, Isis offered non-officer employees an opportunity to exchange certain of their existing out-of-the-money stock options for new options with exercise prices at the then-current market value. These options are required to be accounted for as variable stock options in accordance with Financial Accounting Standards Board Interpretation No. 44 ("FIN 44"), *Accounting for Certain Transactions Involving Stock Compensation—an Interpretation of APB Opinion No. 25*. Isis reported the resulting compensation expense in its statements of operations. As of December 31, 2002, option holders had exchanged all of these options, or the options had expired. As of December 31, 2005 all of the exchanged, unexpired options were fully vested.

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program"). The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options vest over three years beginning on January 1, 2003 and expire on December 31, 2008. Isis accounts for the affected options, until all these options have been exercised or cancelled, using variable accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded non-cash compensation benefit of $544,000 and $6,000 in 2005 and 2004, respectively, and will continue to account for the affected options using variable accounting. These amounts are included in Compensation benefit related to stock options on the Consolidated Statements of Operations and include compensation expense related to non-employee options of $13,000 and $2,000 for 2005 and 2004, respectively.

Isis has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense, except for compensation expense primarily related to the affected options from the 2000 and 2003 option exchange programs, for the Isis stock option plans and the employee stock purchase plan ("ESPP").

1. Organization and Significant Accounting Policies (Continued)

Had Isis determined compensation expense consistent with SFAS 123, Isis would have reported the following pro forma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	2005	2004	2003
Net loss applicable to common stock—as reported	$ (72,401)	$ (142,864)	$ (95,690)
Net loss applicable to common stock—pro forma	$ (76,660)	$ (148,994)	$ (98,971)
Basic and diluted net loss per share—as reported	$ (1.15)	$ (2.52)	$ (1.73)
Basic and diluted net loss per share—pro forma	$ (1.22)	$ (2.63)	$ (1.79)

For purposes of pro forma disclosures, Isis estimated the fair value of each option grant and ESPP purchase rights on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Stock Options			ESPP		
	2005	2004	2003	2005	2004	2003
Risk free interest rate	4.2%	3.0%	2.5%	3.8%	4.2%	4.3%
Dividend yield	0%	0%	0%	0%	0%	0%
Volatility	57.4%	60.5%	58.0%	53.4%	57.2%	49.5%
Expected Life	4.8 years	4.8 years	4.5 years	6 months	6 months	6 months

The weighted average fair value of options granted was $5.51 for 2005, $6.58 for 2004, and $5.70 for 2003. The weighted average fair value of the ESPP purchase rights was $4.59, $4.67, and $4.46 for 2005, 2004, and 2003, respectively.

Comprehensive loss

SFAS 130, *Reporting Comprehensive Income* ("SFAS 130") requires Isis to display comprehensive loss and its components as part of Isis' 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 equity that are excluded from net loss. Specifically, SFAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which Isis reports separately in stockholders' equity, to be included in accumulated other comprehensive loss. Comprehensive loss for the years ended December 31, 2005, 2004 and 2003 has been reflected in the Consolidated Statements of Stockholders' Equity.

Segment Information

Isis operates in two separate segments; Drug Discovery and Development and its Ibis division. In accordance with SFAS 131, *Disclosure about Segments of an Enterprise and Related Information*, Isis provides segment financial information and results for Drug Discovery and Development and its Ibis division based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different

1. Organization and Significant Accounting Policies (Continued)

assumptions or allocation methods could result in materially different results by segment. Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Impact of recently issued accounting standards

In November 2005, the Financial Accounting Standards Board issued FASB Staff Position FAS 115-1, "*The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*", which provides guidance on determining when investments in certain debt and equity securities are considered impaired, whether that impairment is other-than-temporary, and on measuring such impairment loss. FSP 115-1 codifies the guidance set forth in EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*, issued in March 2004. FSP 115-1 also includes accounting considerations subsequent to the recognition of other-than-temporary impairment and requires certain disclosure about unrealized losses that have not been recognized as other-than-temporary impairments. FSP 115-1 is effective for reporting periods beginning after December 15, 2005 and Isis will adopt FSP 115-1 on January 1, 2006. Isis does not believe the adoption of FSP 115-1 will have a material impact on its financial statements.

In May 2005, the FASB released Statement of Financial Accounting Standard ("SFAS") No. 154, "*Accounting Changes and Error Corrections-a replacement of APB Opinion No. 20 and FASB Statement No. 3*". FAS 154 requires retrospective application to prior periods' financial statements for any changes in accounting principle, unless it is impracticable to determine either the period-specific effects or the cumulative effect of the change. The statement defines retrospective application as the application of a different accounting principle to prior accounting periods as if that principle had always been used or as the adjustment of previously issued financial statements to reflect a change in the reporting entity. The statement also requires that a change in depreciation, amortization, or depletion method for long-lived, non-financial assets be accounted for as a change in accounting estimate affected by a change in accounting principle. The statement carries forward, without change, the guidance contained in Opinion 20 for reporting the correction of an error in previously issued financial statements and a change in accounting estimate. In accordance with the new rule requirements, Isis will adopt FAS 154 for any accounting changes or corrections of errors on January 1, 2006. Isis does not expect the adoption of FAS 154 to have a material impact on its consolidated financial position, results of operations, or cash flows.

On December 16, 2004, the FASB issued SFAS 123(R), *"Share-Based Payment"* which requires companies to expense the estimated fair value of employee stock options and similar awards. On April 14, 2005, the U.S. Securities and Exchange Commission adopted a new rule amending the compliance dates for FAS 123(R). In accordance with the new rule, the accounting provisions of FAS 123(R) will be effective for Isis on January 1, 2006.

Isis will adopt the provisions of FAS 123(R) using a modified prospective application. The modified prospective application will apply to new awards and to awards that are outstanding on the effective date and are subsequently modified or cancelled. Compensation expense for outstanding awards for which the

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1. Organization and Significant Accounting Policies (Continued)

requisite service had not been rendered as of the effective date will be recognized over the remaining service period using the compensation cost calculated for pro forma disclosure purposes under FAS 123.

As permitted by FAS 123, Isis currently accounts for share-based payments to employees using Opinion 25's intrinsic value method and, as such, generally recognizes no compensation cost for employee stock options. Accordingly, the adoption of FAS 123(R)'s fair value method may have a significant impact on its results of operations, although it will have no impact on its overall financial position. Isis cannot predict at this time the impact of adoption of FAS 123(R) because it will depend on levels of share-based payments granted in the future. However, had Isis adopted FAS 123(R) in prior periods, the impact of that standard would have approximated the impact of FAS 123 as described in the disclosure of pro forma net income and earnings per share in Note 1 to the consolidated financial statements. FAS 123(R) also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow as required under current literature. This requirement will reduce net operating cash flows and increase net financing cash flows in periods after adoption. While Isis cannot estimate what those amounts will be in the future, as a result of its accumulated losses to date, Isis has not recognized a benefit of tax deductions in excess of recognized compensation cost in operating cash flows.

In November 2004, the FASB issued SFAS No. 151, *"Inventory Costs"*, an amendment of ARB No. 43, Chapter 4. This statement amends the guidance in ARB No. 43 Chapter 4, *Inventory Pricing*, to clarify the accounting for abnormal amounts of idle facility expense, freight, handling costs, and wasted material (spoilage). Paragraph 5 of ARB No. 43, Chapter 4, previously stated that " . . . under some circumstances, items such as idle facility expense, excessive spoilage, double freight, and rehandling costs may be so abnormal to require treatment as current period charges . . ." This statement requires that those items be recognized as current-period charges regardless of whether they meet the criterion of "so abnormal." In addition, this statement requires that allocation of fixed production overheads to the costs of conversion be based on the normal capacity of the production facilities. The provisions of this statement will be effective for inventory costs during the fiscal years beginning after June 15, 2005. Isis does not believe that the adoption of this statement will have a material impact on its financial condition or results of operations.

2. Investments

Isis invests its excess cash in United States Government securities and debt instruments of financial institutions and corporations with strong credit ratings. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of debt securities held by Isis as of December 31, 2005:

Less than 1 year	92%
1 - 3 years	8%
Total	100%

2. Investments (Continued)

Isis has an ownership interest of less than 20% each in two public and two private companies it conducts business with, and accounts for them under the cost method of accounting according to APB 18. The companies are Alnylam and ATL, which are publicly-traded, and Santaris Pharma A/S ("Santaris") and OncoGenex, which are privately-held. In determining if and when decreases in market value of Isis' equity positions below their cost are other-than-temporary, Isis examines historical trends in stock prices, the financial condition and near term prospects of the issuers, and Isis' current need for cash. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the current period operating results to the extent of the decline. See *Note 1—Organization and Significant Accounting Policies* for a discussion of impairment losses incurred in 2005 and 2004.

The following is a summary of Isis' investments accounted for as available-for-sale securities (in thousands):

December 31, 2005	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. corporate debt securities	1 or less	$ 62,778	$ 7	$ (28)	$ 62,757
U.S. Treasury securities and obligations of U.S. government agencies	1 or less	20,578	—	(146)	20,432
Total short-term investments		83,356	7	(174)	83,189
U.S. corporate debt securities	1 to 2	185	—	(3)	182
U.S. Treasury securities and obligations of U.S. government agencies	1 to 3	7,552	—	(184)	7,368
Total long-term investments		7,737	—	(187)	7,550
Subtotal		91,924	7	(361)	$ 90,739
Equity securities					
Short-term portion		3,026	1,835	(167)	4,694
Long-term portion		3,806	1,835	—	5,641
Subtotal		$ 6,832	$ 3,670	$ (167)	$ 10,335
		$ 97,925	$ 3,677	$ (528)	$ 101,074

2. Investments (Continued)

December 31, 2004	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. corporate debt securities	1 or less	$ 27,564	$ —	$ (121)	$ 27,443
U.S. Treasury securities and obligations of U.S. government agencies	1 or less	14,715	—	(98)	14,617
Total short-term investments		42,279	—	(219)	42,060
U.S. corporate debt securities	1 to 2	6,715	—	(47)	6,668
U.S. Treasury securities and obligations of U.S. government agencies	1 to 3	28,169	—	(264)	27,905
Total long-term investments		34,884	—	(311)	34,573
Subtotal		77,163	—	(530)	76,633
Equity securities					
Short-term portion		3,629	2,713	(129)	6,213
Long-term portion		4,738	569	—	5,307
Subtotal		8,367	3,282	(129)	11,520
		$ 85,530	$ 3,282	$ (659)	$ 88,153

Investments considered to be temporarily impaired at December 31, 2005 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		Greater than 12 months of temporary impairment		Total temporary impairment	
		Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
U.S. corporate debt securities	9	$ 8,549	$ 23	$ 1,177	$ 8	$ 9,726	$ 31
U.S. Treasury securities and obligations of U.S. government agencies	22	5,993	19	21,807	311	27,800	330
Total Debt Securities	31	14,542	42	22,984	319	37,526	361
Equity securities	1	1,178	167	—	—	1,178	167
Total temporarily impaired securities	32	$ 15,720	$ 209	$ 22,984	$ 319	$ 38,704	$ 528

Isis believes that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. Isis anticipates full recovery of amortized cost with respect to these securities at maturity.

3. Long-Term Obligations and Commitments

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

	December 31, 2005	December 31, 2004
Lilly $100 million loan	$ —	$ 95,000
Standard operating debt	20,158	32,181
5 1/2% convertible subordinated notes	125,000	125,000
Capital leases and other obligations	2,592	6,741
Total	$ 147,750	$ 258,922
Less: current portion	(7,835)	(10,546)
Less: Lilly debt classified as deferred revenue	—	(11,765)
Total Long-Term Obligations	$ 139,915	$ 236,611

Convertible Partner Debt

Lilly

In August 2001, Lilly made available to Isis a $100 million loan to fund the research collaboration. The loan was interest-free and payable, at Isis' option, in cash or its common stock at $40 per share in August 2005. The loan provided for quarterly draw-downs by Isis. As of December 31, 2004, Isis had drawn down $95.0 million. During the first quarter of 2005, Isis drew the remaining $5.0 million available on the loan facility. In August 2005, Isis converted this loan into 2.5 million shares of its common stock. Isis accounted for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan agreement was entered into. Isis carried the net present value of the draw-downs as a long-term obligation and recorded interest expense over the term of the loan. The difference between the cash received and the present value of the loan represented value Lilly gave Isis to help fund the research collaboration. Isis accounted for this difference as deferred revenue and recognized it as research and development revenue under collaborative agreements over the period of performance. At December 31, 2004, the balance in long-term obligations related to this loan was $83.2 million, and the balance in deferred revenue was $11.8 million. As a result of the conversion, at December 31, 2005, there was no balance in long-term obligations or deferred revenue related to this loan.

Standard Operating Debt

In December 2003, Isis obtained a $32.0 million term loan from Silicon Valley Bank. The term loan is secured by substantially all of Isis' operating assets, excluding intellectual property, real estate, and certain equity investments. The term loan bears interest at the prime rate less applicable discounts (7.0% at December 31, 2005), is payable in equal monthly payments of principal and interest, matures in December 2008, and is convertible at the election of Isis to a fixed rate at the then-applicable prime rate plus 1.25%. The term loan is subject to certain liquidity and other covenants, including a requirement that Isis maintain a minimum balance in an account at the lending bank at all times equal to the outstanding balance of the loan. Isis was in compliance with these covenants as of December 31, 2005 and 2004. Isis used the proceeds of the loan to pay partner debt in 2004. The carrying value of this loan at December 31, 2005 and 2004 was $20.2 million and $26.1 million, respectively, which approximated fair value.

3. Long-Term Obligations and Commitments (Continued)

In December 2002, Isis obtained a credit facility evidenced by promissory notes of up to $6.7 million from a bank to refinance two existing notes, secured by Isis' real property. During 2005, Isis sold the real property and paid the notes in full. The carrying value of this loan at December 31, 2005 and 2004 was $0 and $6.1 million, respectively, which approximated fair value. (*Note 8—Restructuring Activities).*

Convertible Subordinated Notes

In May 2002, Isis completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. Isis includes the issuance costs in the balance sheet under Deposits and Other Assets and is amortizing these issuance costs to interest expense over the life of the debt. The subordinated notes mature in 2009 and bear interest at 5.5%, which is payable semi-annually. The notes are convertible, at the option of the note holders, into approximately 7.5 million shares of common stock at a conversion price of $16.625 per share. At both December 31, 2005 and 2004, the principal and accrued interest outstanding on the notes was $125.0 million and $1.1 million, respectively. The fair value of the subordinated notes was $110.5 million and $104.9 million as of December 31, 2005 and 2004, respectively. Isis did not include these convertible notes in the computation of diluted net loss per share because the effect would be anti-dilutive.

Capital Leases and Other Obligations

At December 31, 2005 and 2004, Isis had approximately $2.6 million and $5.8 million outstanding, respectively, under various capital equipment leases, which bear interest at rates ranging from 7.25% to 8.78% and mature at various dates through 2008. At December 31, 2005 and 2004, Isis had approximately $160,000 and $900,000, respectively, under various contractual obligations. *(Note 6—Collaborative Arrangements and Licensing Agreements).*

Annual debt and other obligation maturities at December 31, 2005 are as follows (in thousands):

2006	$ 7,835
2007	7,528
2008	7,387
2009	125,000
2010	—
Total	$ 147,750

3. Long-Term Obligations and Commitments (Continued)

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through September 2020. Three of the building leases have two extension options for five years each. In connection with the sale of our 28,704 square foot manufacturing facility, the Company leased back the property 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 future contractual obligations of this lease are included in the operating lease caption of the Contractual Obligations table shown above. The lease provides Isis an option to extend the lease for up to two five-year periods. In connection with the lease, Isis executed a stand by letter of credit for $500,000. Annual future minimum payments under capital and operating leases as of December 31, 2005 are as follows (in thousands):

	Operating Leases	Capital Leases
2006	$ 3,458	$ 1,571
2007	2,491	869
2008	1,699	190
2009	1,627	0
2010	1,231	0
Thereafter	10,896	0
Total minimum payments	$ 21,402	$ 2,630
Less amount representing interest		(197)
Present value of future minimum payments		$ 2,433
Less current portion		(1,425)
Long-term portion		$ 1,008

Rent expense for the years ended December 31, 2005, 2004, and 2003 was $2.6 million, $3.1 million, and $3.2 million, respectively. Cost of equipment under capital leases at December 31, 2005 and 2004 was $23.9 million, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2005 and 2004 was approximately $19.7 million and $16.9 million, respectively.

4. Stockholders' Equity

Preferred Stock

Isis is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2005 and 2004, there was no Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible Exchangeable 5% Preferred Stock shares outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series B Convertible Exchangeable 5% Preferred Stock

In June 2004, the holder of the Company's Series B Convertible Exchangeable Preferred Stock transferred its shares to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend, thereby reducing future dilution of

approximately 86,000 shares of Isis common stock. Isis also cancelled a warrant the holder of the Company's Series B Convertible Exchangeable Preferred Stock held to purchase 14,881 shares of Isis

4. Stockholders' Equity (Continued)

common stock. In addition, a warrant the holder of the Company's Series B Convertible Exchangeable Preferred Stock held to purchase 215,000 shares of Isis common stock, expired unexercised in April 2004.

Series C Junior Participating Preferred Stock

In December 2000, Isis 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 Isis 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 Isis 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 Isis' common stock, the Rights permit the holders (except the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share 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 the Isis Board of Directors to redeem

Common Stock

At December 31, 2005 and 2004, Isis had 100,000,000 shares of common stock authorized, of which 72,201,505 and 57,447,333 were issued and outstanding, respectively. As of December 31, 2005, total common shares reserved for future issuance was approximately 24,784,985.

The above amount includes 12 million shares of common stock issued in August 2005. Isis raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from the Company's 60-day average trading price. Investors in the financing also received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share. The net proceeds from the offering were $48.2 million.

Additionally, Isis converted the $100.0 million Lilly loan into 2.5 million shares of the Company's common stock. The impact to the balance sheet was a reduction in long term debt and an increase in stockholders' equity.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis' Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to its employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. The 1989 Plan does not allow Isis to grant stock bonuses or restricted stock awards and prohibits Isis from repricing any options outstanding under the plan unless the Company's stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year

4. Stockholders' Equity (Continued)

period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At December 31, 2005, a total of 4,032,000 options were outstanding, options to purchase 2,157,000 shares were exercisable, and 4,122,000 shares were available for future grant.

2000 Broad Based Equity Incentive Plan

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the option holder's employment or service as a consultant, employee or director. At December 31, 2005, a total of 3,588,000 options were outstanding, 3,116,000 shares were exercisable, and 1,976,000 shares were available for future grant.

In the event of:

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

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. In addition, as of December 31, 2005, approximately 3,588,000 stock awards granted under the 2000 Plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' 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 Isis' non-employee directors. The name of the resulting new

4. Stockholders' Equity (Continued)

plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 600,000 shares of common stock authorized for issuance. 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, 2005, a total of 360,000 options were outstanding, 180,000 of the shares issued under this plan were exercisable and 131,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 2003 through December 31, 2005 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
Outstanding at December 31, 2002	9,256	$ 3.75 to $26.65	$ 11.34
Granted	2,724	$ 3.12 to $7.85	
Exercised	(35)	$ 4.00 to $6.81	
Terminated	(3,734)	$ 3.75 to $26.65	
Outstanding at December 31, 2003	8,211	$ 3.12 to $26.65	$ 8.66
Granted	2,163	$ 4.30 to $9.50	
Exercised	(508)	$ 3.12 to $8.15	
Terminated	(1,199)	$ 3.75 to $22.19	
Outstanding at December 31, 2004	8,667	$ 3.12 to $26.65	$ 8.34
Granted	1,571	$ 2.86 to $5.90	
Exercised	(32)	$ 3.12 to $5.15	
Terminated	(2,227)	$ 3.12 to $26.65	
Outstanding at December 31, 2005	7,979		$ 7.86

The following table summarizes information concerning currently outstanding and exercisable options (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Price	Number Outstanding As of 12/31/05	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/05	Weighted Average Exercise Price
$2.86 - $ 5.76	1,467	5.09	$ 4.93	960	$ 5.08
$5.80 - $ 6.50	1,480	6.15	$ 5.90	179	$ 6.23
$6.59 - $ 6.81	1,773	6.10	$ 6.79	1,309	$ 6.79
$6.82 - $ 9.63	1,796	5.68	$ 7.93	1,567	$ 7.99
$9.75 - $22.83	1,463	4.05	$ 14.00	1,439	$ 13.97
	7,979			5,454	

Employee Stock Purchase Plan

In 2000, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan and Isis reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the 2000

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4. Stockholders' Equity (Continued)

Employee Stock Purchase Plan, resulting in a total of 800,000 shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. During 2005, 222,049 shares were purchased and issued under this plan to employees at prices ranging from $3.36 to $4.67 per share. At December 31, 2005, 50,944 shares were available for purchase under this plan.

Warrants

In 2002, Isis issued a warrant to purchase 6,304 shares of common stock to Elan for the achievement of a development milestone related to the HepaSense joint venture between Isis and Elan. As of December 31, 2005, this warrant remained outstanding at an exercise price of $59.48 per share. The warrant expires April 25, 2007.

In connection with the August 2005 private placement financing, investors received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.2395 per share. The warrants issued in the private placement provide a call right in favor of Isis to the extent that the price per share of Isis's common stock exceeds $14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. Isis cannot exercise this call right prior to August 2008.

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

The fair value of the warrants was estimated using the Black-Scholes option-pricing model ("Black Scholes") with the following assumptions: no dividends, a risk-free interest rate of 4.2%, a contractual life of 5 years and volatility of 54%. The fair value of the Warrants was estimated to be $7.6 million on the closing date of the transaction. In the fourth quarter of 2005, the warrant liability was re-measured and the resulting amount of $5.6 million was reclassified into stockholders' equity. The change in the warrant liability was recorded as interest income. The $2.0 million change in fair value of the warrants was recorded as an increase in interest income in the statements of operation in 2005. (*Note 11—Private Placement Financing*)

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5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2005 and 2004 are shown below (in thousands). Isis recognized valuation allowances of $270.5 million and $283.7 million for 2005 and 2004, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2005	2004
Deferred tax assets:		
Capitalized research expense	$ 40,465	$ 43,132
Net operating loss carryforwards	185,788	189,148
Research and development credits	36,782	33,966
Deferred revenue	617	5,998
Accrued restructuring	9,213	13,335
Other, net	6,537	7,525
Total deferred tax assets	279,402	293,104
Deferred tax liabilities:		
Intangible Assets	(8,907)	(9,393)
Total deferred tax liabilities	(8,907)	(9,393)
Total net deferred tax assets	270,495	283,711
Valuation allowance for deferred tax assets	(270,495)	(283,711)
Net deferred tax assets	$ —	$ —

At December 31, 2005, approximately $7.2 million of the valuation allowance for deferred tax assets related to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2005, Isis had federal, foreign and California tax net operating loss carryforwards of approximately $510.5 million, $1.0 million and $120.0 million, respectively. Isis also had federal and California research credit carryforwards of approximately $25.0 million and $17.5 million, respectively.

The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years California loss carryforwards. Unless previously utilized, the expiration of the federal tax loss carryforwards begins in 2007. The research credit carryforwards begin expiring in 2006, unless utilized. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. The California tax loss carryforwards begin expiring in 2006, unless utilized.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of Isis' net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%. Isis believes that changes in ownership have occurred, but believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. Collaborative Arrangements and Licensing Agreements

Antisense Drug Discovery Collaborations

Amgen

In December 2001, Isis entered into a three-year collaboration with Amgen, Inc. to discover new antisense drugs. Amgen had the right to develop and commercialize antisense drugs resulting from the collaboration. Under the terms of the agreement, Isis was entitled to receive milestone payments upon key clinical, research and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. During 2004, Isis earned revenue of $783,000 related to quarterly research support and progress research milestones under this drug discovery collaboration. In December 2004, Isis' collaboration with Amgen ended in accordance with its terms.

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly, which included four key components.

- Lilly purchased $75.0 million of Isis' common stock at $18 per share.
- Isis licensed to Lilly rights to Affinitak, which Lilly decided to discontinue funding. Lilly paid Isis $25.0 million in upfront fees for Affinitak and reimbursed Isis for Isis' Affinitak development costs. During 2003, Isis earned $11.1 million related to the reimbursement of Affinitak costs. Isis earned no revenue related to Affinitak in 2004 or 2005.
- The companies entered into a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases and a related gene functionalization and target validation collaboration to determine the function of up to 1,000 genes.
- Lilly provided Isis a $100 million loan to fund its obligations under the research collaboration.

In August 2005, Isis extended the research collaboration with Lilly for approximately 24 months to focus on a select number of targets. During the extension, Isis and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis will use collaboration funds to support its scientists and Lilly will support Lilly scientists.

- *LY2181308*—As part of the collaboration, Lilly licensed LY2181308, Isis' antisense inhibitor of survivin, in 2002. To date, Isis has earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308, including the $1.5 million milestone payment Isis earned in November 2004 when Lilly initiated Phase 1 clinical trials of LY2181308. Isis will receive additional milestone payments aggregating up to $25.0 million if LY2181308 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.
- *LY2275796*—Lilly also licensed LY2275796, an antisense inhibitor of eIF-4E, which was discovered through the research collaboration. Isis earned a $750,000 payment from Lilly for the license. In January 2006, Lilly initiated clinical trials of LY2275796 for which Isis received a $750,000 milestone payment. Isis will also receive additional milestone payments aggregating up to $19.5 million if LY2275796 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.

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6. Collaborative Arrangements and Licensing Agreements (Continued)

- *STAT-3*—As part of the recent extension, Isis is exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis is working closely with Lilly to advance an improved STAT-3 candidate into development. Isis will receive milestone payments of up to $28.0 million as an antisense drug targeting STAT-3 advances through various stages of development, and royalties on future product sales of this drug.
- *Antisense Drug Discovery*—The extended collaboration provides Lilly access to Isis' patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries.

In connection with the extension, Isis converted the $100 million loan that Lilly provided to Isis into 2.5 million shares of the Company's common stock. In connection with the extension and the conversion, Lilly agreed not to sell the conversion shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestone payments and royalties in the event of a stock price decline.

Isis' relationship with Lilly historically provided several revenue sources, including research funding related to the $100.0 million research loan, development milestones similar to the milestones for LY2181308 and LY2275796, and revenue related to Affinitak. During 2005, 2004 and 2003, Isis generated revenue from its relationship with Lilly totaling $10.8 million, $15.7 million, and $30.9 million, respectively, which comprised 27%, 37%, and 62%, respectively, of Isis' total revenue during those same periods.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes of Taiwan to identify antisense candidates targeting the coronavirus associated with Severe Acute Respiratory Syndrome, or SARS. The collaboration entitled Isis to an upfront payment, milestone payments, and the potential for future funding. During 2003, Isis earned revenue under this collaboration of $2.0 million, comprised of $1.0 million for an upfront payment and $1.0 million related to the achievement of certain milestones. The milestones related to the identification of second generation antisense drugs that inhibit SARS virus replication and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs as specified under the agreement. Isis earned no revenue during 2004 or 2005 under this collaboration. This collaboration has ended in accordance with its terms.

The Ludwig Institute; Center for Neurological Studies

In October 2005, Isis entered a collaboration agreement with the Ludwig Institute, the Center for Neurologic Study (CNS) and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis and other neurodegenerative diseases. Under this agreement, Isis agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

6. Collaborative Arrangements and Licensing Agreements (Continued)

Pfizer, Inc

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis received a technology access fee of $1.0 million. In 2005, Isis earned milestone payments of $1.2 million through the collaboration. Pfizer will also pay Isis additional milestone payments for the achievement of key research, clinical, regulatory and sales milestones, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, Isis will earn milestone payments totaling up to $25.6 million. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration.

Singapore Economic Development Board

In November 2003, Isis received a grant of up to $8.0 million over three years from the Singapore Economic Development Board ("Singapore EDB"), which was intended to fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS. In connection with this grant, Isis established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary of Isis Pharmaceuticals, Inc. During 2004, Isis earned revenue of $1.5 million from this grant.

As part of the Company's reorganization, Isis decided to close its research and development laboratory in Singapore during the first quarter of 2005 and terminate its agreement with the Singapore EDB. Isis received $1.5 million in cash payments under this $8.0 million grant from the Singapore EDB and does not anticipate any additional payments, or additional revenue, under the agreement.

Satellite Company Collaborations

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. The program Isis licensed to Achaogen resulted from research conducted in Isis' Ibis division to identify drugs to treat antibiotic-resistant infections.

In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to the Company $1.5 million of Achaogen Series A Preferred stock. Isis has not yet determined a value for the Achaogen stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, Isis will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate

6. Collaborative Arrangements and Licensing Agreements (Continued)

relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. For each drug Alnylam develops under this alliance, the potential milestone payments total $3.4 million and are payable to Isis upon the occurrence of specified development and regulatory events. Isis will retain rights to a limited number of RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. In addition, Alnylam and Isis will share the proceeds of any licenses Alnylam grants under its previously announced Interfe*Rx* program that include sublicenses to Isis' patents. Isis agreed to provide Alnylam with access to its resources for development and commercialization of RNAi therapeutics, including process development, bioanalytic methods, quality control and manufacturing. Isis also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed Isis 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. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If Isis develops or commercializes an RNAi-based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties. For each drug we develop under this alliance, the potential milestone payments total $3.4 million and are payable upon the occurrence of specified development and regulatory events. As of December 31, 2005, Isis did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Isis' Alnylam alliance provides the Company with an opportunity to realize substantial value from its pioneering work in antisense mechanism and obigonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery. For example, in October 2005, Isis earned $3.7 million associated with the inclusion of Isis' technology in Alnylam's collaboration with Novartis. In addition, Isis has the potential to earn additional revenue in the form of milestones and royalty payments on drugs which utilize the Isis technology sub-licensed by Alnylam to Novartis. In 2004, Isis earned $500,000 from Alnylam for the inclusion of Isis' technology in Alnylam's ocular alliance with Merck.

During 2005 and 2004, Isis generated revenue from its relationship with Alnylam totaling $3.7 million and $5.5 million, respectively, representing 9% and 13%, respectively, of the Company's total revenue.

In September 2004, Isis recorded a non-cash loss on investment of $5.0 million related to the impairment of its equity investment in Alnylam. The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. Isis' balance sheet at December 31, 2005 and 2004, includes a short-term investment at carrying value amounts of approximately $3.5 million and $2.0 million, respectively, and a long-term investment at carrying value of $3.5 million and $3.9 million, respectively. During 2005, Isis sold a portion of its Alnylam stock for cash proceeds of $2.6 million. Isis still holds more than 580,000 shares of Alnylam's stock.

6. Collaborative Arrangements and Licensing Agreements (Continued)

Antisense Therapeutics Ltd., Inc.

In December 2001, Isis licensed its compound, ATL1102 to Antisense Therapeutics Limited, a publicly-traded company listed on the Australian Stock Exchange. Isis was responsible for the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug. In June 2004, ATL announced the results of a Phase 1 clinical trial of ATL1102, in which ATL1102 was well tolerated. In December 2004, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis. In light of the publicly announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL suspended the trial in March 2005 to convene an advisory group to consider the potential development path for ATL1102. In January 2006, ATL received approval to restart the Phase 2 trial for patients with relapsing-remitting multiple sclerosis. In addition, Isis is participating with ATL in a five-year antisense drug discovery and development collaboration. ATL pays Isis for access to its antisense expertise and for research and manufacturing services Isis may provide to ATL during the collaboration. ATL has the option to license additional drugs from Isis. Additionally, ATL will pay Isis royalties on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expire in 2008. Isis valued its initial ownership at $2.8 million, and is recognizing revenue based on this amount over the term of the agreement. For the years ended December 31, 2005, 2004 and 2003, Isis recorded revenue of $698,000, $1.4 million, and $811,000, respectively, related to this collaboration. As of December 31, 2005, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was approximately 11%. If all of ATL's options, including Isis', were exercised, Isis' ownership in ATL would be approximately 14%. Isis' balance sheets at December 31, 2005 and 2004 included a short-term investment at fair market value of $1.2 million and $3.8 million, respectively, related to this equity investment.

6. Collaborative Arrangements and Licensing Agreements (Continued)

Ercole Biotech, Inc.

In May 2003, Isis and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, the two parties cross-licensed their respective splicing-related intellectual property. As part of this collaboration, Isis granted Ercole a license to its Bcl-x molecule and certain of its chemistry patents. In addition, Isis took an equity ownership position in Ercole, with the initial funding in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. Isis also has the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000, respectively in exchange for a convertible note. Isis expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement.

iCo Therapeutics, Inc.

In August 2005, Isis 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, such as diabetic macular edema age-related macular degeneration and diabetic retinopathy, caused by the formation and leakage of new blood vessels. iCo paid Isis a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note, which will convert into iCo stock upon iCo's completion of a qualified financing. Isis has recognized a valuation allowance of $250,000 to offset the note as realization of this asset is uncertain. iCo will also pay Isis milestone payments totaling up to $23.2 million for the achievement of key clinical and regulatory milestones, and 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 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain.

OncoGenex Technologies Inc.

In November 2001, Isis established a drug development collaboration with OncoGenex Technologies Inc., a privately-held biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize the anti-cancer antisense drug, OGX-011. Isis shares in the costs of developing OGX-011. In exchange, Isis shares in any revenue generated by OncoGenex for OGX-011. In September 2003, the companies expanded their drug development collaboration, to include the development of a second anti-cancer antisense drug, OGX-225. Under the terms of the collaboration, during 2003, OncoGenex paid Isis an upfront fee and Isis acquired an ownership interest in OncoGenex of less than 10%. In addition, OncoGenex will pay to Isis milestone payments totaling up to $3.5 million for the achievement of key clinical and regulatory milestones, and

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6. Collaborative Arrangements and Licensing Agreements (Continued)

royalties on product sales. As of December 31, 2005, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, Isis further broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. In April 2005, OncoGenex selected its first drug under this expanded partnership, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid

Isis an upfront fee with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay Isis 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.

For the years ended December 31, 2005 and 2004, Isis earned revenue of $2.7 million and $669,000, respectively, related to its collaboration with OncoGenex. Isis' balance sheets at December 31, 2005 and 2004 include a long-term investment of $750,000 related to this equity investment, reflecting the value of Isis' initial investment. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in OncoGenex has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value. As of December 31, 2004, Isis' balance sheet included deferred revenue of $1.6 million with corresponding finished goods inventory of $1.4 million on its balance sheet related to an agreement to supply clinical trial material to OncoGenex for which Isis had continuing obligations. In 2005, Isis satisfied these continuing obligations, and as such, recognized the $1.6 million in revenue and related costs of $1.4 million.

Rosetta Genomics, Inc.

In January 2006, Isis initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the

collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Santaris Pharma A/S

In November 1998 and September 2000, Isis entered into license agreements with Santaris, a privately-held company, formerly Pantheco A/S, a privately-held company. The agreement was amended in May 2003. Under the terms of the amended and restated license agreements, Isis licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to Isis' approval. Santaris has agreed to pay Isis royalties on any products developed under the license.

As part of its original license agreements with Pantheco, Isis received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock.

6. Collaborative Arrangements and Licensing Agreements (Continued)

After the merger and as of December 31, 2005 and 2004, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheets at December 31, 2005 and 2004 included a long-term investment of $625,000, respectively, related to this equity investment, reflecting the value of Isis' initial investment. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in Santaris has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

Sarissa, Inc.

In February 2005, Isis licensed an anti-cancer antisense drug to Sarissa, Inc., a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a well-known drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Sarissa paid Isis a $1.0 million upfront fee with a convertible note, which will convert into Sarissa stock upon Sarissa's completion of a financing. Isis has recognized a valuation allowance of $1.0 million to offset the note as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for the achievement of key clinical and regulatory milestones, and royalties on any product sales of this drug. Under the terms of the agreement, Sarissa is solely responsible for preclinical and clinical development of the drug.

Licensing Agreements and Royalty Factoring Agreements

Drug Royalty Corporation

In December 2004, Isis sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. ("DRC). In exchange for this sale, DRC paid Isis $7.0 million in October 2005 and agreed to pay Isis an additional $17.0 million over the next two years. Under the terms of the agreement, Isis and DRC share the royalty rights on Macugen through 2009. After 2009, Isis retains all royalties for Macugen under its Eyetech agreement. Under the agreement, through 2009, DRC will receive the royalties on the first $500.0 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between $500.0 million and $1.0 billion. Isis retains 90 percent of all royalties on annual sales in excess of $1.0 billion and 100 percent of all royalties after 2009. Isis has retained all milestones payable to Isis by Eyetech under the companies' original license agreement.

As part of the sale, Isis agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten percent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to Isis through the default date minus the total of any royalties received by DRC through the default date. To date, DRC has received $3.7 million in royalties. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, Isis fails to meet a minimum liquidity requirement equal to the then outstanding balance on its loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus its cash burn over the most recent three months. As collateral for its obligations under the sale agreement, Isis

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6. Collaborative Arrangements and Licensing Agreements (Continued)

granted DRC a first priority security interest in the patents licensed by Isis to Eyetech under the license agreement and in the license agreement itself.

Eyetech Pharmaceuticals, Inc.

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., a wholly-owned subsidiary of OSI Pharmaceuticals, Inc., certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for the treatment of wet age-related macular degeneration, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay Isis milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis.

During 2004, Isis earned $4.0 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Isis' 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. In 2005, Isis earned no revenue from Eyetech.

Hybridon, Inc.

In May 2001, Isis entered into an agreement with Hybridon under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to Isis' suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, Isis paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in Isis common stock before May 2003. In return for access to Isis' patents, Hybridon agreed to pay Isis $6.0 million in Hybridon common stock before May 2004. In September 2001 and October 2001, Isis issued to Hybridon 357,143 shares of its common stock valued at $5.0 million and 500,000 shares of its common stock valued at $10.0 million, respectively. In May 2002, Hybridon issued to Isis 1,005,499 shares of its common stock valued at $1.3 million and paid Isis $700,000 in cash. In August 2002, Hybridon and Isis cancelled the remaining reciprocal financial obligations related to this agreement. The cancellation of the obligations resulted in a decrease to Isis' carrying value for the license in the amount of $500,000. Isis' balance sheet at December 31, 2005 and 2004 reflected a licensing asset, net of amortization, of $19.5 million and $21.3 million, respectively. Isis' balance sheet at December 31, 2004 also reflected a short-term investment at fair market value of $474,000, related to this agreement. During 2004 and 2005, Isis sold its short term investment in Hybridon for net proceeds of approximately $665,000.

6. Collaborative Arrangements and Licensing Agreements (Continued)

Integrated DNA Technologies, Inc.

In March 1999, Isis licensed certain antisense patents from Integrated DNA Technologies, Inc. ("IDT"), a leading supplier of antisense inhibitors for research. These patents are useful in functional genomics and in making certain antisense drugs. In December 2001, Isis expanded this license agreement to allow Isis to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, Isis paid IDT $4.9 million through December 31, 2005. Isis will pay IDT royalties on drugs utilizing the technology IDT licensed to Isis.

In addition, in December 2001 Isis established a long-term research-scale antisense inhibitor supply agreement with IDT. In this supply agreement IDT agreed to manufacture research-scale antisense inhibitors and research reagents to Isis' specifications. Isis paid IDT $5.0 million toward the future purchase of antisense inhibitors. During the fourth quarter of 2004, Isis recorded a non-cash charge of $4.2 million to write off this unused portion as part of its restructuring activities (*Note 8—"Restructuring Activities"*).

Ibis Division

To develop the TIGER biosensor system and applications, Isis' Ibis division has received contracts and grants from a number of government agencies, including DARPA, the DHS, the CDC, the FBI and the NIAID, a part of the NIH. Each of these agencies represents a significant source of funding for Isis' TIGER program. As of December 31, 2005, Isis had earned $47.9 million in revenue under itsr government contracts and grants and had an additional $8.4 million committed under its existing contracts and grants. In 2005, Isis' Ibis scientists advanced application development for the TIGER biosensor system through contracts with its government partners in the areas of biowarfare defense, microbial forensics, epidemiological surveillance and pharmaceutical process control.

Biowarfare Defense

The earliest application of Isis' TIGER biosensor system to be funded by the government focused on bioweapons detection. In March 2004, Isis' Ibis division received a two-year contract from DARPA under a subcontract from SAIC to further develop the TIGER biosensor system to identify infectious agents in biological warfare attacks. As part of this program, Ibis successfully demonstrated proof-of-principle of the TIGER biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis delivered its first TIGER biosensor system to USAMRIID for use in biowarfare defense.

Microbial Forensics

Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through an award from the FBI, Ibis is continuing its ongoing development of the Microbial Rosetta Stone (MRS) informational databases on microbial agents. The MRS program is a database of biological threat agents, their DNA sequences and effects, that law enforcement officials can use to confer

6. Collaborative Arrangements and Licensing Agreements (Continued)

deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis deployed its second TIGER biosensor system to the DHS's National Bioforensic Analysis Center for use in bioforensics.

Epidemiological Surveillance

Isis' Ibis division continues to develop with its government partners applications for its TIGER biosensor system to rapidly identify, monitor and control infectious diseases. Specifically, in August 2005 Ibis received a three-year grant worth up to $4.9 million from the NIAID, a part of the NIH. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections using the TIGER biosensor system. In addition, in September 2003, Ibis received a three-year grant for up to $6.0 million from the CDC to develop and apply its TIGER technology to the surveillance of human infectious disease in the United States. Ibis expects to deploy a third TIGER biosensor system to the CDC later this year under this contract. In addition, we are currently working with the Naval Health Research Center using the TIGER biosensor system in respiratory disease surveillance and have analyzed hundreds of samples on the TIGER system at our facility. We plan to move the system hardware to the Navy's new laboratory facility, when it's finished.

Pharmaceutical Process Control

Government agencies such as the NIAID have engaged Ibis to develop applications to improve the safety of biological pharmaceutical products, such as vaccines. In 2004, Ibis received funding from the NIAID to develop a TIGER application to specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates.

Joint Ventures

Elan Corporation

Isis and Elan formed Orasense, a joint venture to develop technology for the formulation of oral drugs, and HepaSense, a joint venture to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus, or HCV, during 1999 and 2000, respectively. In late 2002, Elan concluded its participation in both of the related collaborations. Pursuant to a June 2004 agreement, Isis acquired Elan's minority interest in Orasense and HepaSense. As part of the agreement, Isis eliminated all future royalties to Elan related to these joint ventures**.** As of December 31, 2005 and 2004, Isis had no receivable or funding obligation related to Orasense or HepaSense. On July 25, 2005, Isis dissolved the Hepasense, Ltd. subsidiary. In 2004, Orasense incurred approximately $811,000 in research and development expenses through the date of Isis' acquisition of Elan's minority interest in Orasense.

7. Segment Information and Concentration of Business Risk

Segment Information

The Company reports its financial results in two reportable segments, Drug Discovery and Development, and its Ibis division. Segment operating loss includes research and development, general

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

and administrative expenses, and other charges attributable to the segment. Costs excluded from the segments consist of compensation expense (benefit) related to stock options and restructuring activities.

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

The Ibis division generates revenue from grants and contracts from United States government agencies, including DARPA, the DHS, the CDC, the FBI and the NIAID, a part of the NIH. Isis' Ibis division has developed a revolutionary system, called TIGER, that can simultaneously identify thousands of infectious organisms in a sample, without needing to know beforehand what might be present in the sample. Ibis plans to commercialize the TIGER biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

The following is information for net sales and operating income by segment for the years ended December 31, 2005 and 2004.

December 31, 2005	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 16,817	$ 11,793	$ —	$ 28,610
Licensing and royalty	11,523	—	—	11,523
Total segment revenue	$ 28,340	$ 11,793	$ —	$ 40,133
Loss from operations	$ (48,297)	$ (2,228)	$ (6,657)	$ (57,182)

	Drug	Ibis	Corporate	Total

December 31, 2004	Discovery and Development			
Revenue:				
Research and development	$ 21,684	$ 10,933	$ —	$ 32,617
Licensing and royalty	10,007	—	—	10,007
Total segment revenue	$ 31,691	$ 10,933	$ —	$ 42,624
Loss from operations	$(82,135)	$ (3,297)	$ (32,421)	$ (117,853)

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

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	2005	2004	2003
Partner A	27%	37%	62%
Partner B	14%	18%	16%
Partner C	9%	13%	0%
Partner D	17%	0%	0%

During 2005, 2004, and 2003, Isis derived approximately 30%, 28%, and 20%, respectively, of its revenue from agencies of the United States Government, including approximately 14%, 18%, and 16%, respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 39%, 13%, 12% and 12% of contract receivables at December 31, 2005. Contract receivables from four significant partners comprised approximately 30%, 20%, 17% and 10% of contract receivables at December 31, 2004.

8. Restructuring Activities

During the fourth quarter of 2004, Isis recorded a $32.4 million charge for restructuring activities resulting from its strategic decision to reorganize and focus its resources on key programs. The 2004 charge for restructuring activities consisted of non-cash write-downs of tangible and intangible assets that the Company considered to be non-essential to its new focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. For the year ended December 31, 2005, Isis recorded $7.0 million in costs associated with its restructuring activities, net of the gain on the sale of property of $1.5 million discussed below. In January 2005, Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of the Company's research and development laboratory in Singapore.

In connection with the consolidation of its U.S. facilities, during 2005 Isis completed the sale of its real properties located at 2292 Faraday Avenue, 2280 Faraday Avenue and 2282 Faraday Avenue, all in Carlsbad, California. The real properties included three buildings, two of which Isis primarily used for office space and laboratory space and the third which Isis uses for manufacturing. After repaying approximately $5.8 million of debt, which was secured by the properties, and after deducting commissions and other expenses, Isis received net proceeds of approximately $7.9 million for the sale of the properties. Isis included a net gain of approximately $1.5 million in restructuring activities in 2005.

8. Restructuring Activities (Continued)

Pursuant to SFAS No. 146, *"Accounting for Costs Associated with Exit or Disposal Activities,"* the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at December 31, 2005 (in thousands).

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2004	$ —	$ —	$ —	$ —	$ —
Accrued and expensed	1,709	3,751	910	590	6,960
Charged against accrual	853	3,751	145	464	5,213
Balance at December 31, 2005	$ 856	$ —	$ 765	$ 126	$ 1,747

9. Employee Post Employment Benefits

Isis has an employee 401(k) salary deferral plan, covering all domestic employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($14,000 and $18,000 in 2005 for employees under 50 years old and over 50 years old, respectively). Isis made approximately $404,000, $478,000 and $463,000 in matching contributions for the years ended December 31, 2005, 2004 and 2003, respectively.

10. Affiliate Supplementary Disclosure

Orasense

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. Additionally, Isis regained all rights to ISIS 104838, the compound that Elan and Isis were developing within Orasense. In June 2004, Isis acquired Elan's minority interest in Orasense and HepaSense and eliminated all future royalties to Elan related to the technology for the formulation of oral drugs developed within the Orasense collaboration. As a result, Isis owned 100% of Orasense and HepaSense at December 31, 2004. Isis dissolved the Hepasense subsidiary in July 2005. At December 31, 2005, Isis owned 100% of Orasense. In 2004, Orasense incurred approximately $811,000 in research and development expenses through the date of Isis' acquisition of Elan's minority interest in Orasense.

11. Private Placement Financing

In August 2005, the Company raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from the Company's 60-day average trading price. In addition, investors in the financing received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share. The net proceeds from the offering were $48.2 million. The warrants issued in the transaction provide a call right in favor of the Company to the extent that the price per share of the Company's common stock exceeds $14.41 per share for 20 consecutive trading days, subject to certain circumstances. The Company cannot exercise this call right prior to August 2008.

11. Private Placement Financing (Continued)

Pursuant to the terms of the registration rights agreement entered into in connection with the above transaction, within defined timelines the Company was required to file with the SEC a registration statement under the Securities Act of 1933, as amended, covering the resale of all of the common stock purchased and the common stock underlying the warrants. The registration rights agreement further provides that if a registration statement is not filed, or does not become effective, within the defined time period, then in addition to any other rights the holders may have, the Company would be required to pay each holder an amount in cash, as liquidated damages, equal to 1% per month of the aggregate purchase price paid by such holder in the private placement for the common stock and warrants then held. The registration statement was filed within the allowed time, and was declared effective by the SEC on November 1, 2005. As a result, the Company was not required to pay any liquidated damages in connection with the initial registration.

Because of the potential to pay liquidated damages, Isis allocated a portion of the offering proceeds to the warrants based on their fair value in accordance with EITF 00-19, "Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,". The related registration statement was declared effective by the SEC within the contractual deadline and the Company incurred no penalties. The adjustments for EITF 00-19 had no impact on the Company's working capital, liquidity or business operations.

12. Legal Proceedings.

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, that purports to license certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the '830 patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. In October 2005, we filed our answering statement. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position. Ajinomoto and Isis agreed to a bifurcated arbitration process in which the arbitrator would first hear contract arguments and will then hear the patent arguments, if necessary, at a later date. The contract argument portion of the arbitration proceeding took place on February 22, 2006. We expect a ruling from the arbitrator on the first part of this proceeding in the middle of April 2006.

Isis estimates that the potential range of loss on this claim is zero to $2.1 million, and believes it is reasonably possible, not probable, that it will ultimately pay any amounts to Ajinomoto related to this claim. As such, Isis has not recorded a loss related to this claim as of December 31, 2005.

13. 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, 2005, and 2004 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2005 Quarters				
Revenue	$ 7,442	$ 10,592	$ 7,458	$ 14,641
Operating expenses(1)	30,949	23,515	19,602	23,249
Loss from operations(1)	(23,507)	(12,923)	(12,144)	(8,608)
Net loss applicable to common stock(1)	$ (29,658)	$ (19,659)	$ (15,172)	$ (7,912)
Basic and diluted net loss per share(3)	$ (0.52)	$ (0.34)	$ (0.24)	$ (0.11)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2004 Quarters				
Revenue	$ 12,303	$ 9,843	$ 9,093	$ 11,385
Operating expenses(2)	34,638	31,183	31,473	63,183
Loss from operations(2)	(22,335)	(21,340)	(22,380)	(51,798)
Net loss(2)	(26,306)	(25,949)	(32,708)	(57,540)
Accretion of dividends on preferred stock	(181)	(180)	—	—
Net loss applicable to common stock(2)	$ (26,487)	$ (26,129)	$ (32,708)	$ (57,540)
Basic and diluted net loss per share(3)	$ (0.47)	$ (0.47)	$ (0.57)	$ (1.00)

(1) Includes charges related to restructuring activities of $7.0 million incurred during the year ended December 31, 2005.

(2) Includes charges related to restructuring activities of $32.4 million incurred during the quarter ended December 31, 2004.

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

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

Orasense, Ltd., a Bermuda Limited Company

PerIsis I Development Corporation, 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 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) of Isis Pharmaceuticals, Inc. and in the related Prospectuses of our reports dated March 7, 2006, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc.'s management's assessment of the effectiveness of internal control over financial reporting, and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2005.

/s/ ERNST & YOUNG LLP

San Diego, California
March 13, 2006

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;
2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;
3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):
   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: March 16, 2006

/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: March 16, 2006

/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, 2005, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: March 16, 2006

/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.