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, 2004

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

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

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☒ No ☐

The approximate aggregate market value of the voting common stock held by non-affiliates of the registrant, based upon the last sale price of the common stock reported on the National Association of Securities Dealers Automated Quotation National Market System was $286,390,779 as of June 30, 2004.*

The number of shares of voting common stock outstanding as of March 3, 2005 was 57,527,898.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Portions of the registrant's definitive Proxy Statement to be filed on or about April 11, 2005 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 26, 2005 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 51 to 55 incorporates several documents by reference as indicated therein.

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* Excludes 7,230,336 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, 2004. 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, the financial position of Isis Pharmaceuticals, Inc. 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 Isis' clinical 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 technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. 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 the section of Item 1 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.
TAXOTERE® is a registered trademark of Aventis.
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 implicated in disease. Interference with RNA can keep the body from producing proteins that are involved in disease. We are the leader in exploiting RNA as a target for drugs, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, or oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. We also use our antisense technology internally and in collaborations with pharmaceutical companies to rapidly and efficiently identify and prioritize attractive gene targets for drug discovery. Within our Ibis division, we are expanding on our RNA expertise by creating a system that can rapidly and accurately identify a broad range of infectious organisms with a single test. Our ongoing development of this technology and a system related to this technology has been funded primarily by agencies within the United States government.

We successfully commercialized our first antisense drug, Vitravene. Vitravene demonstrates our ability to meet Food and Drug Administration, or FDA, and European regulatory requirements, and to commercially manufacture antisense drugs. We and our partners currently have 10 antisense products in preclinical and clinical development, the majority of which are in Phase I or Phase II human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, metabolic and cardiovascular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. In addition, 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 prior chemistries. Specifically, these drugs offer the potential for improved safety, increased potency and a longer half-life, which correlates with durability of therapeutic response and the potential for less frequent dosing. Physicians may be able to dose our second-generation drugs as infrequently as once every two weeks to once a month. We are also making progress on developing oral formulations of our second-generation antisense drugs. Our oral formulations may increase the commercial value of our antisense drugs.

Within our Ibis division we have invented technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. We have applied the TIGER technology to develop a system to identify from a sample a broad range of infectious organisms, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. During 2004, we advanced the development of our TIGER system to include application development for epidemiological surveillance and biological products screening. These applications represent the first of many we plan to develop to enhance the TIGER system's commercial value and opportunity in the government, research, medical and diagnostic markets.

To date, we have earned $40.1 million in revenue from several government agencies, including up to $37.5 million for the development of TIGER and $2.6 million to discover small molecule drugs, under contracts valued at up to $66.3 million. These agencies include the Defense Advanced Research Projects Agency, or DARPA, the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, or NIH, the Centers for Disease Control, or CDC, the Federal Bureau of Investigation, or FBI, and the United States Army Medical Research Institute of Infectious Diseases, or USAMRIID.

We have a broad patent portfolio covering our products and technologies. We have rights to more than 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. 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 we grant them. Licensing partnerships may include traditionally structured antisense drug discovery and development collaborations with large pharmaceutical companies like Lilly and Amgen.

Antisense technology allows us to repeatedly produce more drug candidates than we can afford to develop on our own. As a result, we have extended our licensing partnerships to include our satellite company strategy in which we provide our expertise and intellectual property position in RNA-based therapeutics to industry partners that are interested in developing RNA-based

therapeutics. Because these companies work closely together with us, with the common goals of advancing the technology and/or pipeline, we sometimes refer to these companies as satellite companies. These partnerships allow us to benefit from our partners' expertise and highly focused research efforts, while our partners benefit from our experience in RNA-based drug discovery and development and access to our intellectual property. In return for providing companies with access to our technology, we receive an ownership interest in the resulting products and/or in the companies. Through these relationships we are expanding the reach and potential of antisense therapeutics and participating in the success of multiple companies and products. This provides us with the opportunity to create a much broader antisense pipeline than we could afford to develop on our own, while minimizing our financial obligations. We have implemented this integral component of our strategy through our partnerships with Alnylam Pharmaceuticals, Inc., or Alnylam; Antisense Therapeutics, Ltd., or ATL; Ercole Biotech Inc., or Ercole; OncoGenex Technologies, Inc., or OncoGenex; Santaris Pharma A/S, or Santaris; and Sarissa, Inc., or Sarissa.

In addition, we have an active intellectual property licensing program in which we license aspects of our intellectual property to companies like Hybridon, Inc., or Hybridon; Integrated DNA Technologies, Inc., or IDT; Roche Molecular Systems, or Roche: atugen A/S, or atugen; and Dharmacon, Inc., or Dharmacon. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc., or Eyetech. In December 2001, we licensed several chemistry patents to Eyetech for the development of Macugen, a drug for the treatment of wet age-related macular degeneration, or AMD, that Eyetech is co-developing and commercializing with Pfizer, Inc., or Pfizer. In 2004, we earned $4.0 million in milestone payments from Eyetech associated with their filing of a New Drug Application, or NDA, for Macugen with the FDA and Eyetech's receipt of marketing clearance for the drug. In January 2005, we sold a portion of our royalty rights in Macugen to Drug Royalty USA., Inc., or DRC, in exchange for aggregate payments of $24 million over the next three years. To date, we have generated nearly $70.0 million from our intellectual property licensing program that helps support our internal drug discovery and clinical development programs.

We incorporated in California in 1989, and in 1991 we reincorporated as a Delaware corporation. Our principal offices are in Carlsbad, California. In November 2003, we established Isis Pharmaceuticals Singapore Pte Ltd, our wholly-owned subsidiary in Singapore. As part of our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology, we decided to close our research and development laboratory in Singapore during the first quarter of 2005.

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 specifically targets disease-causing proteins before the body produces them. 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 bases, or 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 structures 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 receptors 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 drug candidates 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 drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. We have also made significant progress in developing new formulations of antisense drugs, like oral, subcutaneous, intravitreal, aerosol, enema and topical cream that further expand the potential for antisense technology.

Further, we use antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. This information forms the basis of the first step of our antisense drug discovery program. 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.

Small Molecule Antibmicrobial Drug Discovery

Prior to the development of TIGER, our Ibis division focused on discovering novel small molecule antimicrobial drugs. DARPA principally funded this project until 2002, when USAMRIID elected to be the transition partner for a DARPA-sponsored research program to discover small molecule antimicrobial drugs for biological warfare defense. As part of the transition we entered into a three-year, $2.4 million contract with USAMRIID to advance this work. As of December 31, 2004, we had received $2.1 million from the United States government for this program. We expect to allocate limited resources to advance this technology once we complete our work under the USAMRIID contract in the first quarter of 2005. Our goal is to secure a partner for this program.

Ibis Division

Within our Ibis division we have invented technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. We have applied the TIGER technology to develop a system to identify from a sample a broad range of infectious organisms, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. During 2004, we advanced the development of our TIGER system to include application development for epidemiological surveillance and biological products screening. These applications represent the first of many we plan to develop to enhance the TIGER system's commercial value and opportunity in the government, research, medical and diagnostic markets.

TIGER is the product of core technology development and small molecule drug discovery research conducted within our Ibis division. In its early years, Ibis focused on discovering novel small molecule antimicrobial drugs. Ibis' central focus now is to develop and commercialize our TIGER technology.

The advancement of TIGER application development has brought us closer to realizing the commercial potential of this unique and proprietary technology. To continue this progress, we recently hired Michael Treble to head our Ibis division. Mr. Treble's knowledge and expertise in product development and in commercializing research instruments and diagnostic products will complement the expertise and innovation of David J. Ecker, Ph.D., the scientific leader of TIGER technology development.

To develop the TIGER technology and applications, our Ibis division has received contracts from a number of government agencies, including DARPA, the NIAID, part of the NIH, the CDC and the FBI. Each of these agencies represents a significant source of funding for our TIGER program. To date, we have earned $40.1 million in revenue under our government contracts and grants. 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. Our Ibis division has received contracts and grants from numerous government agencies valued at up to $63.2 million.

During 2004 and 2003, revenue generated from agencies of the United States Government totaled 28% and 20%, respectively, of our total revenue. Refer to *Note 7, "Segment Information and Concentration of Business Risk,"* starting on page F-30 of this report on Form 10-K for additional information about our Ibis division.

Approved Product and Products In Development

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

We have designed our drugs in development to treat a variety of health conditions, including inflammatory, metabolic, and cardiovascular diseases, and cancer, and we and our partners are studying them in intravenous, subcutaneous, topical cream, 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' products 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	Launched in the U.S. and Europe (3)	Isis/Novartis Ophthalmics AG(3)
Alicaforsen (ISIS 2302) (E)	ICAM-1	Ulcerative Colitis	Phase II	Isis
ISIS 113715 (P)*	PTP-1b	Diabetes	Phase II	Isis
ISIS 301012 (P)*	apoB-100	High Cholesterol	Phase I	Isis
ISIS 301012 (O)*	apoB-100	High Cholesterol	Preclinical	Isis
ISIS 345794 (P)*	STAT-3	Cancer	Preclinical	Isis

Partner Drugs in Development

Product(1)	Target	Potential Disease Indication(s)	Development Status(2)	Commercial Rights
ATL 1102 (ISIS 107248)(P)*	VLA-4	Multiple Sclerosis	Phase II	ATL
OGX-011 (ISIS 112989) (P)*	Clusterin	Cancer	Phase I/II	OncoGenex / Isis
ATL 1101 (T)*	IGF-1R	Psoriasis	Phase I	ATL
LY2181308 (P) *	Survivin	Cancer	Phase I	Lilly
LY2275796 (P) *	eIF-4E	Cancer	Preclinical	Lilly

* Drugs based on proprietary second-generation chemistry

(1) I = Intravitreal; P = Parenteral; T = Topical; O = Oral; E = Enema

(2) A compound 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 Ophthalmics AG has the exclusive worldwide rights to distribute Vitravene, which it distributes on a limited basis.

The following section provides more detailed descriptions of our approved product and those products in clinical development and the disease indications they target. We also have a significant research program. Our goal for 2005-2006 is to advance at least two new drug candidates from our cardiovascular, metabolic or inflammatory disease research programs into development.

Cytomegalovirus, or CMV Retinitis

Individuals with suppressed immune systems, such as those with AIDS resulting from the HIV virus, are susceptible to opportunistic infections caused by CMV. Among patients with AIDS, CMV retinitis is the primary cause of blindness. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet, cidofovir and fomivirsen (Vitravene).

Vitravene, or fomivirsen—In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Vitravene is an antisense compound that we discovered and developed. Novartis Ophthalmics AG, the eye health unit of life sciences leader Novartis AG, and 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 AG currently offers Vitravene on a limited basis.

Inflammatory Diseases

Our research and development efforts in the therapeutic area of inflammatory diseases focus on identifying and developing antisense inhibitors to proteins such as intercellular adhesion molecule 1, or ICAM-1 and another adhesion molecule called CD49d, which is a subunit of Very Late Antigen-4, or VLA-4. Researchers believe that these proteins are involved in inflammatory diseases.

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 innermost 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 II 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 II 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. We plan to find a strong commercial partner for alicaforsen enema, while planning a Phase III program for the drug.

  Our goals for 2005 - 2006 for alicaforsen enema for ulcerative colitis are to:

  - meet with the FDA to discuss Phase III development plans for the drug; and
  - identify a marketing partner with late-stage development and commercial expertise, and work with that partner to develop and implement a successful Phase III development program.

- ***Crohn's disease***—Crohn's disease is a serious inflammatory disease that affects the entire digestive tract, unlike UC which affects only the colon. A patient with Crohn's disease suffers chronic and often severe episodes of diarrhea, abdominal pain, rectal bleeding and fever. In December 2004, we reported the results of our Phase III 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 will not invest further in the development of alicaforsen for Crohn's disease.

ATL 1102—ATL 1102, formerly called ISIS 107248, 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 ATL 1102 to ATL. Under our agreement with ATL, we completed the required preclinical studies for ATL 1102 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 I clinical trial of ATL 1102, in which the drug was well-tolerated. In December 2004, ATL initiated a Phase IIa clinical trial of ATL 1102 in patients with multiple sclerosis. In March 2005, ATL announced that, although it and the trial investigators are confident that the current ATL 1102 Phase II trial is safe, in light of the recently announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL decided to halt the current trial and convene an advisory group to consider the potential development path for ATL 1102 which may include restarting a Phase II trial program in multiple sclerosis and exploring ATL 1102 as an inhaled asthma treatment. We plan to support ATL's development efforts to determine the potential of ATL 1102 as an effective treatment for multiple sclerosis and asthma.

ATL 1101—ATL 1101 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. Their research has 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. We plan to support ATL's program to explore the activity of ATL 1101 in patients with psoriasis, which includes completing the ongoing study ATL is conducting. 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. Abnormal growth or overproduction of skin cells characterizes psoriasis.

Metabolic Diseases

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—ISIS 113715 is our second-generation antisense inhibitor of the PTP-1b gene for the treatment of type 2 diabetes. An antisense inhibitor of PTP-1b 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 is often difficult to identify small molecule drugs with sufficient specificity to be safe. Antisense allows us to design very specific inhibitors to PTP-1b that do not inhibit other phosphatases.

In May 2003, we initiated a Phase I clinical trial to assess the safety and pharmacokinetic profile of several doses of ISIS 113715 by parenteral administration in 20 healthy volunteers. In September 2003, we reported the results from this Phase I study, in which ISIS 113715 increased insulin sensitivity in normal volunteers. Further, subjects treated with ISIS 113715 did not experience hypoglycemia or excessively low blood sugar, which is an adverse effect observed with many currently available treatments for type 2 diabetes. Based on the results of this Phase I study, we initiated a Phase II clinical trial to further evaluate the drug's ability to regulate blood sugar levels in patients with type 2 diabetes.

Our goals for 2005-2006 for our ISIS 113715 clinical development program for type 2 diabetes are to:

- demonstrate safety of the drug as a single agent in patients with type 2 diabetes to support longer-term dosing;
- define the optimal dose and schedule to support future clinical trials;
- advance ISIS 113715 into additional clinical trials to evaluate longer-term dosing; and
- explore the drug in patients who are taking oral anti-diabetic therapies.

Our development plans for 2005-2006 to meet these goals are to:

- report the results from our ongoing Phase II single agent trial in patients with type 2 diabetes;
- report the results following 12 weeks of dosing from a single agent trial in patients with type 2 diabetes; and
- initiate dosing in patients with type 2 diabetes who are also taking oral anti-diabetic therapy.

Cardiovascular Diseases

We are pursuing the discovery and development of antisense drugs for cardiovascular diseases such as 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 American adults have high cholesterol levels.

ISIS 301012—ISIS 301012 is a second-generation compound 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, or LDL, the "bad" cholesterol. In preclinical studies, ISIS 301012 reduced total cholesterol, very low-density lipoproteins, or VLDL, LDL, and triglyceride levels, all of which are keys to managing heart disease. We initiated a Phase I study in late 2003 in volunteers with borderline elevated cholesterol. The goal of this initial study was to measure the safety and pharmacokinetic profile of ISIS 301012, and its ability to reduce several components of cholesterol. In 2004, we announced preliminary data from this trial, which demonstrated ISIS 301012 produced dose-dependent, rapid and prolonged reductions of its target, apoB-100, in LDL, in VLDL, and in total cholesterol levels in volunteers with borderline elevated cholesterol. We have also demonstrated that an oral formulation of ISIS 301012 reduces cholesterol in animals.

For 2005-2006, our goals for ISIS 301012 clinical development programs for lowering high cholesterol, both the subcutaneous injection and oral formulations, are to:

- understand the optimal dose and schedule for the drug as a single agent;
- prepare to initiate combination studies with atorvastatin, and other drugs;
- define the oral bioavailability of ISIS 301012 and demonstrate reduction of its target, apoB-100, and cholesterol reduction in man;
- advance ISIS 301012 into additional clinical trials to evaluate longer-term dosing; and
- explore other indications, such as apheresis, that may offer shortened routes to commercialization.

Our development plans for 2005-2006 to meet these goals are to:

- report final results from our ongoing Phase I single agent study in normal volunteers with borderline elevated cholesterol at an appropriate scientific meeting;
- initiate a Phase II trial to evaluate dose and dose schedule in patients with high cholesterol;
- initiate a pharmacokintetic study to evaluate the addition of ISIS 301012 to statin therapy;
- initiate a Phase 2 study in patients with high cholesterol who are also taking statins; and
- initiate a Phase I trial of the oral formulation of ISIS 301012 in volunteers with normal cholesterol levels.

Cancer

We, together with our partners, are pursuing the development of antisense drugs for the treatment of a variety of cancers. In clinical trials, we and our partners have observed evidence of activity of our anti-cancer drugs. In addition, patients tolerated our compounds well, with none of the serious side effects, such as bone marrow or immune system suppression, gastrointestinal distress or hair loss, associated with standard cancer chemotherapies.

OGX-011—OGX-011, formerly called ISIS 112989, is a second-generation antisense inhibitor of clusterin, which we are co-developing and commercializing with OncoGenex, a Canadian oncology-focused research and development company. We have 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 I 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. We plan to support OncoGenex's expansion of OGX-011 development into additional cancer therapeutic areas through the completion of this second Phase I trial evaluating OGX-011 in combination with TAXOTERE in solid tumors, and with the initiation of Phase II clinical trials in patients with lung, breast and prostate cancers in 2005.

LY2181308—We licensed our preclinical anti-cancer candidate, LY2181308, formerly ISIS 23722, 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. Under the two-year agreement, we and Lilly collaborated to discover antisense drugs to inhibit specific gene targets associated with cancer. The cancer collaboration built on the broad, strategic alliance the companies forged in August 2001, to among other things, discover antisense drugs in the areas of inflammatory and metabolic diseases. The compound targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin is one of the most highly overexpressed proteins in cancers. Our researchers and collaborators have shown that inhibiting 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 from Lilly in the development of LY2181308. LY2181308 is the first compound from this partnership to advance to clinical trials. In November 2004, Lilly initiated Phase I clinical trials of LY218308 in cancer patients, for which we earned a second $1.5 million milestone.

LY2275796—LY2275796 is the second anti-cancer drug candidate we have licensed to Lilly and is currently in preclinical 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.

During 2005 - 2006, we plan to support Lilly's ongoing anti-cancer antisense research and development programs through the progression of the above Phase I trial of LY2181308 in patients with cancer and the continued preclinical development of LY2275796 for cancer. Further, we plan to support Lilly's oncology franchise by providing new antisense drug candidates for licensing consideration by Lilly.

ISIS 345794—ISIS 345794 is the latest compound to emerge from our cancer research program and is in preclinical development for cancer. Signal Transducer and Activator of Transcription 3, or STAT-3 is a protein that regulates cell division and growth and prevents cell death. In preclinical studies, we have demonstrated that antisense inhibition of STAT-3 significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer. Based on these findings, we selected ISIS 345794 for clinical development.

Recently Discontinued Products

ISIS 104838 produced positive disease responses in patients with rheumatoid arthritis, according to results of two Phase II studies. While we are encouraged by the performance of this drug, in light of the strong competition in this market and the significant investment required to bring the first oral anti-TNF product to market, we elected to discontinue development of this drug. In addition, we have discontinued development of ISIS 14803, a first-generation drug for the treatment of hepatitis C.

In October 2004, we reported the results of a second Phase III clinical trial of Affinitak in combination with Gemzar and cisplatin in patients with non small cell lung cancer, or NSCLC. Findings from this trial, which was sponsored by Lilly, were similar to the results of the initial Isis-sponsored Phase III study of Affinitak for NSCLC, in which Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. As a result of these trials, we will not invest further in the development of Affinitak.

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 drug candidates. The goal of our target-based research programs is to identify antisense and small molecule drug candidates 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 products 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.

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 Ercole and Alnylam.

RNAi is an antisense mechanism that involves using a small interfering RNA, or siRNA, as a method to target an 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 are pursuing opportunities to license these patents to companies specializing in RNA interference as a therapeutic method.

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 approximately 250-300 known micro-RNA molecules in humans.

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.

Prior to the development of TIGER, our Ibis division focused on discovering novel small molecule antibacterial drugs. We expect to allocate limited resources to advance this technology once we complete our work under the USAMRIID contract in the first quarter of 2005. Our goal is to secure a partner for this program.

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.

Antisense technology allows us to repeatedly produce more drug candidates than we can afford to develop on our own. As a result, we have extended our licensing partnerships to include our satellite company strategy in which we provide our expertise and intellectual property position in RNA-based therapeutics to industry partners that are interested in developing RNA-based therapeutics. Because these companies work closely together with us, with the common goals of advancing the technology and/or pipeline, we sometimes refer to these companies as satellite companies. These partnerships allow us to benefit from our partners' expertise and highly focused research efforts, while our partners benefit from our experience in RNA-based drug discovery and development and access to our intellectual property. In return for providing companies with access to our technology, we receive an ownership interest in the resulting products and/or in the companies. Through these relationships we are expanding the reach and potential of antisense therapeutics and participating in the success of multiple companies and products. This provides us with the opportunity to create a much broader antisense pipeline than we could afford to develop on our own, while minimizing our financial obligations. We have implemented this integral component of our strategy through our partnerships with Alnylam, ATL, Ercole, OncoGenex, Santaris, and Sarissa.

2004 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 2004 and early 2005.

- We formed a strategic alliance with Alnylam to accelerate the development and commercialization of RNAi therapeutics. We earned a $5.0 million technology access fee and a $500,000 payment from our participation in Alnylam's partnering program;

- We received a two-year contract providing up to $19.5 million from DARPA through a contract with SAIC to further the development of our TIGER system to identify infectious agents in biological warfare attacks;

- We were granted three new government contracts valued at up to $10.0 million for the continued development of our TIGER technology;

- We earned $4.0 million in milestone payments from Eyetech associated with their filing of an NDA for Macugen and receipt of marketing clearance for the drug, and 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;

- We earned a $1.5 million Phase I clinical milestone from Lilly for LY2181308, an inhibitor of survivin;
- We earned a $750,000 payment from Lilly for the license of LY2275796, a cancer drug that targets eIF-4E;
- We extended our anti-cancer antisense drug discovery collaboration with Lilly. This oncology relationship builds on a broad, ongoing strategic alliance previously established by Isis and Lilly to discover antisense drugs in the areas of inflammatory and metabolic diseases;
- We jointly developed a new high performance solid support for the manufacture of oligonucleotides with Nitto Denko Corporation of Osaka, Japan. Solid support is the base structure used in the synthesis of oligonucleotides, both antisense, including RNA and DNA-based and RNAi, and aptamer drugs and represents a substantial portion of the cost to manufacture these drugs. The new solid support has the potential to decrease manufacturing costs of oligonucleotide-based drugs, including antisense;
- We acquired Elan Corporation plc's minority interest in Orasense and HepaSense, joint ventures arising out of prior collaborations between Isis and Elan, and eliminated all future royalties to Elan related to the oral delivery platform developed within the Orasense collaboration and to ISIS 14803;
- We expanded our strong intellectual property position in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of miRNA from the Max Planck Society;
- We licensed an anti-cancer antisense drug to Sarissa, Inc., in exchange for a $1.0 million represented by a debt instrument which will convert into Sarissa stock upon Sarissa's successful completion of a venture capital financing; and
- We broadened our antisense drug development partnership with Oncogenex to allow for the development of two additional second-generation antisense anti-cancer drug candidates.

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly, including 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 has decided to discontinue funding.
- We initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related gene functionalization and target validation collaboration to determine the function of up to 1,000 genes. Key achievements and developments under this collaboration include:
  - In 2002, Lilly and we expanded our antisense drug discovery collaboration to include oncology and the license of LY2181308, our antisense inhibitor of survivin for which we earned a $1.1 million license fee. Under the two-year agreement, we and Lilly collaborated to discover antisense drugs to inhibit specific gene targets associated with cancer. The expanded collaboration focused initially on several antisense preclinical compounds, including LY2181308, directed at cellular regulators of cancer cell death, or apoptosis.
  - In April 2003, we earned a $1.5 million milestone from Lilly in the development of LY2181308, the antisense inhibitor of survivin, as part of the research collaboration oncology expansion. LY2181308 is the first compound from the partnership selected by Lilly for clinical development. In November 2004, Lilly initiated Phase I clinical trials of LY218308 in cancer patients, marking a significant milestone in the partnership and triggering a $1.5 million milestone payment from Lilly to us. Our collaboration with Lilly also may generate additional milestone payments aggregating up to $25.0 million based on LY2181308 achieving specified regulatory and commercial milestones.
  - In July 2003, we expanded the cancer research component of our antisense drug discovery collaboration with Lilly to include multiple antisense mechanisms, such as RNAi and alternative splicing, as well as third generation antisense chemistries. We are currently jointly developing follow-on drugs to LY2181308 that work through an RNAi mechanism and that use proprietary Isis chemistries.
  - In May 2004, Lilly and we announced the extension of our antisense drug discovery collaboration in cancer. During this 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. An important component of this extension will be the exploration of potential new anti-cancer drug targets using RNA-directed technologies.

- In September 2004, Lilly licensed from us LY2275796. This second-generation antisense anti-cancer drug candidate targets eIF-4E. We earned a $750,000 payment from Lilly for the license. LY2275796 is the second compound from the partnership to be selected by Lilly for clinical development. Our collaboration with Lilly also may generate additional milestone payments aggregating up to $20.3 million based on LY2275796 achieving specified regulatory and commercial milestones.

- Lilly committed to lend us, interest-free, up to $100.0 million over a four-year period to fund our obligations under the research collaboration. This loan comes due in August 2005. We can repay this loan at our option in either cash or our common stock, at a fixed conversion price of $40 per share.

To date, Lilly has paid or committed to pay us $292.9 million in funding through 2005, including the $100.0 million loan, the $75.0 million equity investment, the $25.0 million in Affinitak up-front license fees, reimbursement for Affinitak development costs and research collaboration license fees and milestones. Of this $292.9 million we had collected $287.9 million as of December 31, 2004. Assuming the success of multiple products from our collaboration with Lilly, we have the opportunity to earn additional future milestones and royalties from Lilly that could be substantial to us.

As part of our relationship with Lilly, in 2003, 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 relationship with Lilly has historically provided several revenue sources, including research funding related to their $100.0 million research loan to us, development milestones similar to the milestones for LY2181308 and LY2275796, and revenue related to Affinitak. During 2004, 2003 and 2002, we generated revenue from our relationship with Lilly totaling $15.7 million, $30.9 million and $45.4 million, respectively, which comprised 37%, 62%, and 57%, respectively, of our total revenue during those same periods. Our current collaboration with Lilly expires in August 2005. Consequently, we anticipate our revenue from Lilly will decrease in 2005.

Antisense Drug Discovery Collaborations

Singapore Economic Development Board

In November 2003, we received a grant of up to $8.0 million over three years from the Singapore Economic Development Board, or EDB, which was intended to fund, in part, the broadening of two of our 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, we established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary of Isis Pharmaceuticals, Inc. As part of our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology, we decided to close our research and development laboratory in Singapore during the first quarter of 2005 and terminate our agreement with the EDB. To date, we have received $1.5 million in cash payments under our EDB grant and do not anticipate receiving any additional payments under the grant.

Industrial and Technology Research Institutes of Taiwan

In June 2003, we initiated a collaboration with ITRI to identify antisense candidates targeting the coronavirus associated with SARS. We conducted the research in exchange for an upfront payment of $1.0 million, milestone payments, and the potential for future funding. In December 2003, we achieved two milestones in our antisense drug discovery partnership with ITRI, for which we received a total of $1.0 million. 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. This collaboration has ended in accordance with its terms.

Amgen

In December 2001, we entered into a three-year collaboration with Amgen to discover new antisense drugs. In December 2004, this collaboration with Amgen ended in accordance with its terms.

Satellite Company Collaborations

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 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.

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 debt instrument, 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 key clinical and regulatory achievements and royalties on any product sales. Sarissa will be solely responsible for preclinical and clinical development of the drug.

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 of these drugs, the potential milestone payments total $3.4 million and are payable 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 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 of these drugs, the potential milestone payments total $3.4 million and are payable upon the occurrence of specified development and regulatory events. As of December 31, 2004, 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 the second quarter of 2004, we earned a $500,000 license fee from Alnylam related to Alnylam's alliance with Merck.

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 Isis believes was primarily a result of financial market conditions related to biotechnology companies.

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.

During 2004, we generated revenue from our relationship with Alnylam totaling $5.5 million, or 13%, of our total revenue.

Ercole Biotech, Inc.

In May 2003, we and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, we cross-licensed our respective splicing-related intellectual property. 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 convertible debt, 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 promissory 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.

Antisense Therapeutics Limited

In December 2001, we licensed ATL 1102, formerly ISIS 107248, to ATL, an Australian company publicly traded on the Australian Stock Exchange. We were responsible for completing the required preclinical studies for ATL 1102 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 I clinical trial of ATL 1102, in which ATL 1102 was well-tolerated. In December 2004, ATL initiated a Phase IIa clinical trial of ATL 1102 in patients with multiple sclerosis. In March 2005, ATL announced that, although it and the trial investigators are confident that the current ATL 1102 Phase II trial is safe, in light of the recently announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL decided to halt the current trial and convene an advisory group to consider the potential development path for ATL 1102, which may include restarting a Phase II trial program for multiple sclerosis and exploring ATL 1102 as an inhaled asthma treatment.

ATL is also developing ATL 1101, an antisense compound targeting IGF-1R for the treatment of psoriasis. ATL recently initiated a Phase I study in patients with psoriasis.

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 is obligated to pay 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%.

OncoGenex Technologies Inc.

In November 2001, we established a drug development collaboration with OncoGenex Technologies Inc., a Canadian oncology-focused research and development company, to co-develop and commercialize OGX-011, formerly ISIS 112989, an anti-cancer antisense drug candidate. 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 I/II studies. OncoGenex has responsibility to perform Phase I clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and to perform Phase I/II clinical trials 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 I 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 April 2003, OncoGenex and we initiated a second Phase I/II trial to evaluate OGX-011 in combination with TAXOTERE in various solid tumors. OGX-011 was our first second-generation antisense anti-cancer drug in clinical trials. We plan to support OncoGenex's expansion of OGX-011 development into additional cancer therapeutic areas through the completion of this second Phase I trial evaluating OGX-011 in combination with TAXOTERE in solid tumors, and with the initiation of Phase II clinical trials in patients with lung, breast and prostate cancers.

In September 2003, we and OncoGenex expanded our antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug candidate, OGX-225. OncoGenex has responsibility for the preclinical and clinical development of the drug. OncoGenex issued us OncoGenex securities as payment for an upfront fee. In addition, OncoGenex agreed to provide to us milestone payments totaling up to $3.5 million for key clinical and regulatory achievements and to pay us royalties on product sales. As of December 31, 2004, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, we broadened our antisense drug development partnership with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drug candidates. Under the terms of the agreement, OncoGenex will be responsible for the preclinical and clinical development of the drug. OncoGenex agreed to pay us an upfront fee, milestone payments for key clinical and regulatory achievements, and royalties on future product sales.

As of December 31, 2004, our ownership interest in OncoGenex was less than 10%.

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 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 common 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 antidilution provisions related to Pantheco's stock. After the merger and as of December 31, 2004, our ownership interest in Santaris was less than 10%.

Antisense Commercialization

Novartis Ophthalmics AG

In 1997, we entered into an agreement with Novartis Ophthalmics AG, formerly CIBA Vision Corporation, granting them exclusive worldwide distribution rights for Vitravene, an antisense compound that we discovered and developed. The terms of the agreement provided for us to receive $20.0 million in pre-commercial fees and milestones. As of December 31, 2001, we had received the full $20.0 million of these pre-commercial fees and milestones. In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Novartis Opthalmics AG launched Vitravene in November 1998. Due to the low incidence of CMV retinitis among patients with AIDS, Novartis AG currently offers Vitravene on a limited basis.

Ibis Collaborations

To develop the TIGER technology and applications, our Ibis division has received contracts from a number of government agencies, including DARPA, the NIAID, part of the NIH, the CDC and the FBI. Each of these agencies represents a significant source of funding for our TIGER program. To date, we have earned $40.1 million in revenue under our government contracts and grants. 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. Our Ibis division has received contracts and grants from numerous government agencies valued at up to $63.2 million.

In 2004, we received three new government contracts valued at up to $10.0 million for the continued development of our TIGER system. A key highlight of these new contracts was funding from the NIAID to develop a TIGER application aimed at ensuring vaccine safety. Currently, there are few tests available that can 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. Successful development of an application to simultaneously identify a broad array of infectious agents in vaccine cell substrates would create a new commercial prospect for our TIGER system.

We receive funding from DARPA through a subcontract with SAIC, on a multi-year project for the ongoing development of TIGER. This project combines our expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal processing capabilities. In March 2004, we entered into a two-year contract with SAIC that provides for up to $19.5 million in funding by DARPA. During 2004 and 2003, revenue from SAIC comprised 18% and 16%, respectively, of our total revenue.

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. Using the grant from the CDC, we expect to develop and provide TIGER technology for CDC projects focused on emerging human infectious disease.

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.

Molecular Biosystems, Inc.

In March 2001, we amended a non-exclusive Patent License Agreement, which we entered into with Molecular Biosystems, Inc. in September 1992. The amendment provided us with a fully paid-up license to certain patents and patent applications in exchange for a one-time payment to Molecular Biosystems of $1.0 million. Molecular Biosystems has since been acquired by Alliance Pharmaceuticals, Inc.

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 have paid IDT $4.2 million through December 31, 2004 and expect to pay IDT an aggregate of $700,000 in 2005 for the license.

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 the fourth quarter of 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

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.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, a publicly-held company, certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense compound intended for use in the treatment of ophthalmic diseases. 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. In December 2002, Eyetech entered into an agreement with Pfizer to develop and commercialize Macugen.

During 2004, we earned from Eyetech $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 also may generate additional milestone payments aggregating up to $2.8 million based on achieving specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication.

Drug Royalty Corporation

In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA, Inc., or DRC, in exchange for aggregate payments of $24 million over the next three 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. Under the agreement, through 2009 DRC will receive 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. 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.

Dharmacon

In May 2004, we entered into a patent license agreement with Dharmacon, a wholly owned subsidiary of Fisher Scientific International, Inc. In order to sell chemically modified RNA for research purposes, Dharmacon licensed from us certain chemistry and method-of-use patents in return for an upfront licensing fee and royalties on reagent sales. Through this agreement, we are able to provide access to our technology to a wide array of academic labs, research institutes and companies practicing this technology while participating financially in Dharmacon's success.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides, like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing 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 have 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.

We have contractual obligations to manufacture clinical trial materials and/or commercial supply for ATL, 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.

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, 2005, we owned or had exclusively licensed more than 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:

- Method claims for the use of RNA/DNA oligonucleotides and other antisense inhibitors, in gene functionalization and target validation, including chemistries, antisense inhibitor designs called "motifs", methods of use of antisense inhibitors and mechanisms of action by which antisense inhibitors inactivate an RNA target;
- Composition of matter claims to core chemistries for chemically modifying oligonucleotides, which cover our rights to the building blocks of our compounds;
- Composition of matter claims to antisense compounds targeted to particular RNA target sequences, which cover our drugs;
- Use claims for using oligonucleotides targeted to particular disease targets, which cover our right to use oligonucleotide-based drugs to treat specific diseases or modulate expression of the target gene;
- Method and composition of matter claims for the formulation and delivery of therapeutic oligonucleotides, which cover our pharmaceutical formulations of our drugs;
- Method claims for the manufacture of oligonucleotides, which cover our new, improved and/or more cost effective ways to manufacture oligonucleotides;
- Composition of matter claims to RNA structural elements, which cover our rights for discovery of small molecules that bind to these RNA structural elements;
- Method claims for analyzing the interaction of small molecules with RNA, which cover our novel discovery methods using mass spectrometry to analyze the interaction of small molecules with RNA;
- Method claims for optimizing the interaction of drug substances with their target molecules, which cover our mass spectrometry-based structural activity relationship discovery methods;
- Method claims for identifying unknown bioagents utilizing mass-spectrometry-based analyses; and
- Method claims for rapidly discovering antisense oligomeric compounds, which cover our rapid throughput method of discovering antisense oligonucleotides.

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 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, or FARs, and agency regulations supplemental to the FARs; 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.

Competition

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

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 is an important competitive factor. 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.

Employees

As of March 3, 2005 we employed approximately 303 individuals, of whom 141 held advanced degrees. These numbers exclude employees impacted by our January 2005 reduction in force, some of who were still employed by us as transition employees or under our salary continuation program. 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 its employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of March 3, 2005:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	59	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, J.D.	49	Director, Executive Vice President, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.	48	Vice President, Antisense Research
Richard K. Brown, Ph.D.	52	Vice President, Business Development
David J. Ecker, Ph.D.	50	Vice President and Scientific Head of Ibis Division
Arthur A. Levin, Ph.D.	51	Vice President, Development
Patricia Lowenstam	58	Vice President, Human Resources and Operations
John McNeil	40	Vice President, Ibis Product Development
Michael J. Treble	58	Vice President and Head of Ibis Division

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 its Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, 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, Axon Instruments, Inc., a developer and manufacturer of novel high-technology devices and software for drug discovery, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents, Northern Arizona University Arts and Sciences Advisory Council, Flagstaff, Arizona, and BIOCOM, San Diego, California. Dr. Crooke is also an adjunct professor of pharmacology at San Diego State University.

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, counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is on the Board of Trustees of the Bishops' School. Ms. Parshall is also a member of American, California and San Diego bar associations.

C. FRANK BENNETT, Ph.D.
Vice President, Antisense Research

Dr. Bennett has served as our Vice President, Antisense Research since June 1995. 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.

RICHARD K. BROWN, Ph.D.
Vice President, Business Development

Dr. Brown joined Isis in June 2001 as President of the GeneTrove program and has been our Vice President, Business Development since January 2003. Prior to joining Isis, Dr. Brown was President of Irori, a company that develops, manufactures and markets combinatorial chemistry and medicinal chemistry products to the pharmaceutical industry. He joined Irori in 1996 and served as President from 1998 to June 2001.

DAVID J. ECKER, Ph.D.
Vice President and Scientific Head, 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. 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.
Vice President, Development

Dr. Levin has served as our Vice President, Development since 1995. 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.

PATRICIA LOWENSTAM
Vice President, Human Resources and Operations

Ms. Lowenstam has served as our Vice President, Human Resources and Operations since January 1995. She joined Isis in August 1992 as our Director, Human Resources and served in that capacity until January 1995. Prior to joining Isis, she held senior management positions in Human Resources with Quotron Systems, Inc., Citicorp, Zale Corporation, and the May Company.

JOHN MCNEIL
Vice President, Ibis Product Development

Mr. McNeil has served as our Vice President, Ibis Product Development since January 2005. Prior to that, he was our Vice President, Informatics since October 1999. Mr. McNeil joined Isis in October 1997 as our Director, Informatics. Prior to joining Isis, Mr. McNeil was President of John McNeil & Co., Inc., and held various positions at SAIC in San Diego from 1989 to 1997, including Manager of the Laboratory Sensors and Automation division.

MICHAEL J. TREBLE
Vice President and Head, Ibis Division

Mr. Treble joined Isis in December 2004 as Head 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 microarray 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.

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.

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

Because drug 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, 2004, we had accumulated losses of approximately $698.4 million and a stockholders' deficit of approximately $72.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from 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 or our partners fail to obtain regulatory approval for our products, 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 drug candidates before a drug candidate 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 drug candidates, 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 candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. 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 candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate 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 product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drug candidates.

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 drug candidates that have not met the primary clinical end points in their initial Phase III studies.

In March 2003, we reported the results of a Phase III 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 III 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 III 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 payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available 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 drug candidates and their potential advantages over competing products;
- The cost and effectiveness of our drug candidates compared to other available therapies;
- The patient convenience of the dosing regimen for our drug candidates; and
- Reimbursement policies of government and third party payors.

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

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 product candidates.

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 III trials, Eli Lilly discontinued its investment in Affinitak.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, 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 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 company 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 drug candidates 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 candidate and, as a result, could delay or otherwise negatively affect the commercialization of a drug candidate.

In addition, the disappointing results of the two Affinitak trials, our Phase III 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 drug candidates could suffer.

We may not successfully develop or derive revenues from our business based on our TIGER system to identify infectious organisms.

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

All of our product candidates are still 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 through at least mid 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:

- the profile and launch timing of our drugs;
- 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
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, 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 we cannot manufacture our products or contract with a third party to manufacture our 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 drug candidates, 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 drug candidates, 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 we fail to compete effectively, our products 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 drug candidates or technologies that are more effective than any drug candidates 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.

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 such 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.

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.

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, 2004, the market price of our common stock has ranged from $4.22 to $9.90 per share. On March 11, 2005 the closing price of our common stock on the Nasdaq National Market was $3.95 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug 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.

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 in connection with the issuance of our securities to Eli Lilly and Company. These registration rights cover approximately 2.5 million shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these securities are converted and the holder exercises its registration rights, it will bring additional shares of our common stock into the market, which 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 Registered Independent 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, or PCAOB, or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

Item 2. Properties.

As of March 3, 2005, we occupied approximately 218,000 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 six buildings in Carlsbad, California. We own three of these buildings and, as of December 31, 2004, these buildings secured approximately $6.1 million of our debt. We lease three of the buildings under lease agreements, of which two leases will expire in 2007 and one will expire in 2010. In February 2003, we completed an expansion of our manufacturing facility to upgrade our existing manufacturing suite and add a second state of the art manufacturing suite.

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, which 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. Ajinomoto also seeks a determination that the license is still in force. We have not yet filed an answer, and a hearing has not yet been set. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position in arbitration.

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
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
2003		
First Quarter	$ 7.55	$ 2.50
Second Quarter	$ 6.85	$ 3.50
Third Quarter	$ 8.05	$ 4.55
Fourth Quarter	$ 7.07	$ 5.20

As of March 3, 2005, there were approximately 1,067 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.

Available Information

We make available, free of charge, on our web site, *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.

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

	Years Ended December 31,				
	2004	2003	2002	2001	2000
Consolidated Statement of Operations Data:					
Revenue (includes amounts for R&D, licensing and royalties)	$ 42,624	$ 49,990	$ 80,179	$ 53,273	$ 37,255
Research and development expenses	$ 118,474	$ 116,963	$ 124,074	$ 83,741	$ 57,014
Net loss applicable to common stock [1]	$ (142,864)	$ (95,690)	$ (73,302)	$ (75,131)	$ (54,699)
Basic and diluted net loss per share	$ (2.52)	$ (1.73)	$ (1.35)	$ (1.70)	$ (1.48)
Shares used in computing basic and diluted net loss per share	56,642	55,463	54,480	44,109	37,023

	Years Ended December 31,				
	2004	2003	2002	2001	2000
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 103,883	$ 215,504	$ 289,353	$ 312,018	$ 127,262
Working capital	$ 82,193	$ 194,004	$ 244,230	$ 280,569	$ 118,568
Total assets	$ 208,425	$ 334,942	$ 438,683	$ 417,061	$ 183,256
Long-term debt and capital lease obligations, less current portion	$ 236,611	$ 213,397	$ 192,893	$ 125,710	$ 102,254
Accumulated deficit	$ (698,447)	$ (555,583)	$ (459,893)	$ (386,591)	$ (311,460)
Stockholders equity (deficit)	$ (72,133)	$ 67,178	$ 155,477	$ 223,099	$ 66,366

(1) Our net loss applicable to common stock includes charges related to restructuring activities of $32.4 million, $1.8 million, $1.4 million, and $1.6 million in 2004, 2003, 2002, and 2000, 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 we have successfully turned our expertise into one marketed product and 10 antisense drugs, which we and our partners are advancing in pre-clinical and clinical development, the majority of which are in Phase I or Phase II human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, metabolic, cardiovascular diseases, and cancer. We and our partners are studying these drugs in intravenous, subcutaneous, topical cream, enema, aerosol, and oral formulations, and we are advancing antisense drugs using second-generation chemistry. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen) in 1998.

To date, we have earned $40.1 million in revenue from several government agencies, including up to $37.5 million for the development of TIGER and $2.6 million to discover small molecule drugs, under contracts valued at up to $66.3 million. These agencies include the Defense Advanced Research Projects Agency, or DARPA, the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, or NIH, the Centers for Disease Control, or CDC, the Federal Bureau of Investigation, or FBI, and the United States Army Medical Research Institute of Infectious Diseases, or USAMRIID. During 2004 and 2003, revenue generated from agencies of the U.S. Government accounted for 28% and 20%, respectively, of our total revenue.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 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. To date, we have generated nearly $70.0 million from our intellectual property licensing program that helps support our internal drug discovery and clinical development programs.

We are pursuing early-stage antisense research programs, including RNA interference, or RNAi, micro-RNA, and alternative splicing through research collaborations and partnerships, like our strategic alliances with Alnylam and Ercole.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. Our proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drug candidates 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 drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. We have also made significant progress in developing new formulations of antisense drugs, like oral, topical cream, subcutaneous, intravitreal, aerosol and enema that further expand the potential for antisense technology.

We and our partners currently have 10 drugs in development, of which three are in Phase II clinical development, four are in Phase I clinical development and three are in preclinical development. Our partners are developing, with our support, five of these ten drugs, which substantially reduces our development costs.

Ibis Division. Within our Ibis division, we have invented a technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. TIGER is the product of core technology development and small molecule drug discovery research conducted within our Ibis division in its early years. Ibis' central focus now is to develop and commercialize our TIGER technology. Prior to the development of TIGER, our Ibis division focused on discovering novel small molecule antibacterial drugs.

As a result of the technological and organizational advancements that we have made during 2004 combined with our future commercialization plans for TIGER and the significant contribution that the division made to Isis' 2004 revenue, and in accordance with the authoritative guidance under SFAS No. 131, *"Disclosure about Segments of an Enterprise and Related Information,"* we believe it is appropriate to present the financial results of our Ibis division as a separate operating segment

from our consolidated results. We refer to this operating segment as our Ibis division. 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.

Recent Event

In December 2004, we made a strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. We announced this decision in January 2005. In the fourth quarter of 2004 we recorded a $32.4 million charge for restructuring activities resulting from this decision, which consisted 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.

We expect to incur additional charges relating to our restructuring activities during the first quarter of 2005, including those associated with employee termination costs, termination of certain contractual obligations, the consolidation of our United States facilities, and the closure of our research and development laboratory in Singapore.

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. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. 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 up-front payments for prior or future expenditures. We recognize revenue related to up-front 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 ATL, Chiron, 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 take quarterly drawdowns against this loan and discount 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. As of December 31, 2004, we had drawn down $95.0 million on this loan. We are accreting 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 represents value Lilly gave to us to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance.

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 milestones 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 to future performance related to the achievement of the milestone. We recognized revenue during 2004 related to milestones achieved under our agreements with Eyetech, Lilly and Singapore EDB.

We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. To date, in two 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 and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty fees 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 also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is 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 the first quarter of 2003, we recorded a non-cash loss on investments of $2.4 million related to the impairment of our equity investments in ATL and Hybridon. We recorded these charges based on declines in market value of the equity investments, as compared to their initial valuations. During the third quarter of 2004, we recorded a non-cash loss on investments of $5.1 million principally 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

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, among other 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 refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. 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 are non-essential to our current focus.

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 second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak to zero. During the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue development of antisense technology.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. 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 costs. 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. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Assets

As disclosed in Note 5 of Notes to the Consolidated Financial Statements, we record a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. 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. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset. As of December 31, 2004, our deferred tax assets and related valuation allowance totaled approximately $283.7 million.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our 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.

Proforma Stock-Based Compensation

We provide proforma net income 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."* or SFAS No. 123. The stock-based compensation expense used in these proforma 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 2005, 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 can not 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, 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 primarily reflects the completion of our Phase III 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 may fluctuate from period to period based on the nature and timing of license fees and milestones 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. Our ability to maintain revenue at current levels will depend on our ability to obtain new revenue sources and expand existing revenue sources in 2005.

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

	Year Ended December 31, 2004	Year Ended December 31, 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	$ 49,990

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 2003. The decrease of $16.9 million reflects the completion of our Phase III 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 I 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 candidate for clinical development.

Our Ibis division generates revenue from grants and contracts from United States government agencies, including DARPA, CDC, FBI, and 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. Our Ibis division has received contracts and grants from numerous government agencies valued at up to $63.2 million. 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.

In order to analyze and compare our results of operations to other 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 to exclude restructuring activities because the costs are directly related to isolated events.

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 II clinical program for alicaforsen enema in patients with ulcerative colitis, and increased spending to support our highest priority second-generation drug candidates, 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. We expect total research and development spending will decrease in 2005 as a result of the completion of our development activities for alicaforsen for Crohn's disease, our decision to discontinue development of ISIS 14803 and ISIS 104838, our strategic reorganization and associated reduction in workforce, consolidation of facilities, and closure of our Singapore location.

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

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

Antisense Drug Discovery

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 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 custom target-validation 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 and cardiovascular disease. The work of our scientists has given us the opportunity to enter into important drug discovery relationships with industry leaders like Lilly and Amgen.

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 in 2005. 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 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

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 candidate 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 I—one year, Phase II—one to two years, and Phase III—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 candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. For example, we recently decided not to initiate additional studies of ISIS 14803 and ISIS 104838. Generally, Phase III clinical trials are the longest, largest and most expensive component of the drug development process. Further, products in Phase III trials represent the most near term possibility of commercial success. In addition, because Phase III 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 I and Phase II programs are really research programs that fuel our Phase III pipeline. When our products are in Phase I or Phase II 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 I" or "in Phase II," 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. For example, during 2003, Lilly reimbursed us for our costs to develop Affinitak. Our partners are developing, with our support, five of our 10 drug candidates, which substantially reduces 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,	
	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 was primarily due to the completion in 2003 of our Phase III 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. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials, and anticipate that such expenses will decrease in 2005 as compared to 2004 as the result of our strategic reorganization and associated reduction in workforce.

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 III 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 III 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 III study of Affinitak for NSCLC. As a result of these data, we will not 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 was primarily due to the completion of our Phase III 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 I and Phase II 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 2003. The increase of $700,000 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 2003. The increase of $2.5 million 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. We expect R&D Support costs to decrease in 2005 as a result of our strategic reorganization and reduction in workforce announced in January 2005.

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

	Year Ended 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 2003. The increase of $300,000 as compared to 2003 was primarily related to our Sarbanes-Oxley Act Section 404 implementation activities. We allocated $924,000 million 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. We expect general and administrative expenses to decrease in 2005 as a result of our strategic reorganization and reduction in workforce announced in January 2005.

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

	Year Ended 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 2003 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. We expect to incur additional charges relating to restructuring activities during the first quarter of 2005, including those associated with employee termination costs, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore. We expect that our cost containment measures will significantly decrease our cash use in 2005 as compared to 2004.

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.

We plan to draw the remaining $5.0 million from Lilly in March 2005, which will bring our total due to Lilly under our loan agreement to $100.0 million. Our loan to Lilly is due in August 2005. We can repay our Lilly research collaboration loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down the remaining amount available under the loan, we could repay the loan for 2.5 million shares of our common stock. We expect to substantially reduce our debt obligations in 2005 as a result of the repayment of our Lilly loan, combined with principal payments we are obligated to make on our loan with Silicon Valley Bank. Accordingly, we expect our interest expense to decrease in 2005.

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 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 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, 2003 and December 31, 2002

Revenue

Total revenue for the year ended December 31, 2003 was $50.0 million, compared to $80.2 million for 2002. The decrease of $30.2 million was primarily due to the reduction in revenue associated with the clinical development of Affinitak and the conclusion of Elan's participation in the Orasense and HepaSense collaborations in late 2002. We did not have revenue associated with Orasense and HepaSense in 2003 as a result of the conclusion of Elan's participation in the joint ventures. New revenue sources not present in 2002 offset, in part, the decreases in total revenue in 2003.

Research and Development Revenue under Collaborative Agreements

Under the category research and development revenue under collaborative agreements, for the year ended December 31, 2003, we earned $49.5 million, compared to $67.8 million for 2002. The decrease of $18.3 million was primarily due to the reduction in revenue associated with the clinical development of Affinitak. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single-study new drug application. New sources of revenue not present in 2002 slightly offset the previously described decreases in revenue. New sources of revenue from our Antisense Drug Discovery collaborations included:

- an upfront fee and milestone payments from ITRI;
- a milestone achieved in the development of LY2181308, as part of our research collaboration oncology expansion with Lilly;
- a milestone achieved in our drug discovery collaboration with Amgen; and
- an upfront fee from the expansion of our antisense drug development partnership with OncoGenex.

New revenue sources from our Ibis division resulted from the expansion of work to continue the advancement of our TIGER technology, which included work for government agencies such as the CDC, FBI, and DARPA. Our work for DARPA continued to be a collaborative effort with SAIC and accounted for approximately 16% and 6% of our revenue in 2003 and 2002, respectively.

Research and Development Revenue from Affiliates

Research and development revenue from affiliates consisted of revenue associated with our two collaborations with Elan, Orasense and HepaSense. Elan concluded its participation in the HepaSense and Orasense collaborations in late 2002, in conjunction with its restructuring efforts. As a result, we reacquired product rights to ISIS 14803 for hepatitis C and the oral formulation of ISIS 104838 from the HepaSense and Orasense joint ventures, respectively. We did not earn revenue from these affiliates in 2003. During 2002, we recognized $8.9 million and $3.0 million as revenue from Orasense and HepaSense, respectively.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $523,000 for the year ended December 31, 2003, compared with $417,000 in 2002.

Operating Expenses

Total operating expenses were $129.0 million and $131.0 million for the years ended December 31, 2003 and 2002, respectively. The decrease of $2.0 million was primarily due to our implementation of an expense reduction plan during the second quarter of 2003, the completion of our development activities for Affinitak, and the termination of our GeneTrove database product offering in November 2002. Increased clinical development expenses for many of our other products and increased costs in the Ibis division partially offset the decrease in operating expenses. Increased expenses of $3.9 million and $430,000 for compensation related to stock options and restructuring activities, respectively, further offset the decrease in operating expenses. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation expense or benefit related to stock options from operating expenses because it is based on the variability of our stock price rather than operations. We also believe that it is important to exclude restructuring activities because these costs are directly related to isolated events.

Research and Development Expenses

For the year ended December 31, 2003, we reported total research and development expenditures of $117.0 million, compared to $124.1 million reported in 2002. Our research and development expenses consisted of costs for antisense drug discovery, antisense drug development, our Ibis division and related R&D Support costs. The antisense drug discovery costs included costs associated with our GeneTrove program. The decrease of $7.1 million in 2003 over 2002 was primarily due to the termination of our GeneTrove product offering and reorganization of the GeneTrove program in November 2002, our implementation of an expense reduction plan in April 2003, and a decrease in our total Affinitak related expenses. Increased clinical development expenses for many of our other products and our increased efforts in the Ibis division offset, in part, our decreases in research and development expenditures.

Antisense Drug Discovery

Antisense drug discovery costs included in research and development expenses for the year ended December 31, 2003 totaled $36.8 million compared to $38.9 million for 2002. The decrease of $2.1 million in 2003 over 2002 was principally a result of our planned expense reductions started in the second quarter of 2003 and the termination of our GeneTrove database product offering and reorganization of the GeneTrove program in November 2002. These decreases were offset in part by the increase in expenses to support our research collaborations with Lilly, Amgen, and ITRI.

Antisense Drug Development

During 2003, we had 11 drug candidates in various stages of development, including two drugs in Phase III clinical trials. In March 2003, we announced the results of our Phase III clinical trial of Affinitak for the treatment of non-small cell lung cancer. The results were not sufficient to support a single study new drug application. Affinitak related expenses decreased in 2003 compared to 2002. We had two Phase III trials of alicaforsen, or ISIS 2302, in people with active Crohn's disease. We conducted one of these studies in North America and the other in Europe. These studies were evaluating the safety and efficacy of alicaforsen. We also had Phase II programs ongoing for five additional products, Phase I programs ongoing for three additional products, and preclinical studies ongoing for one project. In addition, during 2002 and 2003, Lilly reimbursed us for our costs related to our development of Affinitak.

Development costs included in research and development expenses totaled $45.1 million and $55.3 million for the years ended December 31, 2003 and 2002, respectively. The decrease of $10.2 million was primarily due to planned expense reductions started in the second quarter of 2003 driven by a reduction in clinical development activity related to Affinitak. These decreases were offset, in part, by increased clinical development expenses for our other products, mainly alicaforsen for Crohn's disease and several products in Phase II and earlier stages of development.

The planned expense reductions began in April 2003 when we initiated a restructuring effort in response to the disappointing results from our Phase III trial of Affinitak. As a result, we had a small reduction in our workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. We completed our development activities for Affinitak in 2003. As a result, expenditures related to Affinitak decreased from $22.6 million in 2002 to $5.1 million in 2003. The majority of the 2003 expenditures occurred in the first quarter of 2003.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $6.5 million for the year ended December 31, 2003, compared to $4.8 million for the same period of 2002. The increase of $1.7 million was the result of an increase in the number of patients undergoing treatment in our two Phase III trials. These trials were initiated in November 2001 and June 2002.

Expenditures related to our other products in development totaled $29.3 million for the year ended December 31, 2003, compared to $23.1 million for 2002. The increase of $6.2 million in 2003 over 2002 was mainly the result of increased expenses for Phase II trials of alicaforsen in ulcerative colitis, the Phase I trials for ISIS 113715 for type 2 diabetes and preclinical studies and initiation of a Phase I trial of ISIS 301012 for cardiovascular disease.

Ibis

Ibis expenditures for the year ended December 31, 2003 totaled $9.9 million, compared to $8.3 million for 2002. The increase of $1.6 million was primarily related to Ibis' continued performance obligations under its multi-year government contracts with DARPA through our relationship with SAIC, awarded in October 2001, and USAMRIID, awarded in March 2002, and new performance obligations under Ibis' agreement with the CDC, awarded in September 2003, and with various other government agencies. Included as

Ibis expenditures were fixtures and equipment accounted for as pass-through costs that Ibis purchased for government agencies under the contractual terms of their agreements. From June 2000 through June 2002, Ibis also received funding from its collaboration with Pfizer, which ended in June 2002 in accordance with the terms of the agreement.

R&D Support

R&D Support costs for the year ended December 31, 2003 totaled $25.2 million, compared to $21.6 million for 2002. The increase of $3.6 million was primarily due to increases in our research and development efforts related to our efforts to prepare for the manufacture and commercialization of Affinitak in the first quarter of 2003, our increased efforts related to our government contracts and increased depreciation resulting from the completion of laboratory build-outs. Our planned expense reductions initiated in April 2003 offset, in part, the increases in our research and development efforts noted above.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2003 totaled $9.3 million compared to $8.5 million for 2002. This $800,000 increase was primarily a result of an increase in employees and related benefits in the first quarter of 2003. A reduction in the number of employees and a corresponding reduction in expense as a result of the restructuring in April 2003 offset, in part, the increases noted above.

Compensation Related to Stock Options

Compensation expense for the year ended December 31, 2003 was $913,000, compared to compensation benefit of $3.0 million for the year ended December 31, 2002. Compensation expense for 2003 primarily consisted of expense for stock options associated with the employee stock option exchange program we initiated in April 2003. We accounted for options affected by the 2003 option exchange program as variable stock options in accordance with Accounting Principles Board Opinion No. 25, or APB 25, and Financial Accounting Standards Board Interpretation No. 44, or FIN 44. APB 25 and FIN 44 required us to account for these exchange 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 2003 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. The compensation benefit in 2002 represented the reversal of previously recorded compensation expense for stock options accounted for as variable stock options associated with the option exchange program we offered to non-officer employees in January 2000.

Restructuring Activities

In April 2003, we initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, we had a small reduction in our workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, we incurred a restructuring charge of $1.8 million during the second quarter of 2003. We completed the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

In November 2002, we announced the termination of our functional genomics database product offering and the reorganization of our functional genomics program. As a result, we reduced our workforce by approximately 25 people. The restructuring plan included the write-down of certain intellectual property valued at $605,000. As a result of this plan, we incurred a one-time charge of $1.4 million for restructuring activities in the fourth quarter of 2002. We did not recognize any additional restructuring related charges for the year ended December 31, 2003, and completed utilization of the reserve related to this restructuring in the fourth quarter of 2003.

Equity in Loss of Affiliates

In late 2002, Elan concluded its participation in the Orasense and HepaSense collaborations in conjunction with its restructuring efforts. As a result, we regained all rights to ISIS 104838, the compound that Elan and we were developing within Orasense. We also regained all rights to ISIS 14803, the compound that Elan and we were developing within HepaSense.

We did not have equity in loss of affiliates for the year ended December 31, 2003. As mentioned previously, we used the equity method of accounting for our investments in Orasense and HepaSense in 2002. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense as equity in loss of affiliates during 2002. Our equity in loss of affiliates for the year ended December 31, 2002 consisted of $9.5 million for Orasense and $6.5 million for HepaSense.

Investment Income

Investment income for the years ended December 31, 2003 and 2002 was $5.1 million and $8.5 million, respectively. The $3.4 million decrease in investment income in 2003 compared to 2002 was primarily due to our lower cash, cash equivalents and short-term investments balances in 2003 compared to 2002, and a decline in interest rates as a result of then current market conditions.

Interest Expense

Interest expense for the year ended December 31, 2003 was $18.7 million compared to $16.6 million for the same period in 2002. The $2.1 million increase in interest expense in 2003 compared to 2002 was primarily due to a higher average debt balance during 2003 than during 2002. The increase in debt compared to 2002 related primarily to additional drawdowns under our debt agreement with Lilly. 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 May 2002 and July 2002 of higher interest rate debt with proceeds from the issuance, in May 2002, of our 5 ½% convertible notes due in 2009 and 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 retired in the fourth quarter of 2003 consisted of convertible partner debt that carried interest rates ranging from 8.5% to 12%.

In 2003, $7.5 million of the $18.7 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.

Loss on Prepayment of 14% Notes

For the year ended December 31, 2002, we reported a $2.3 million loss on prepayment of debt, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest, on the prepayment of approximately $74.0 million of our 14% Senior Subordinated Notes. No such prepayment occurred in 2003.

Gain on Prepayment of 12% Notes

In July 2002, we used $14.7 million in cash to prepay $19.7 million of 12% convertible debt Elan held. As a result, we reported a $5.0 million gain on prepayment of debt for the year ended December 31, 2002. No such prepayment occurred in 2003.

Net Loss Applicable to Common Stock

For the years ended December 31, 2003 and 2002, we reported a net loss of $95.0 million and $72.2 million, respectively. Our net loss applicable to common stock was $95.7 million for the year ended December 31, 2003, and $73.3 million for 2002, including $694,000 and $1.1 million, respectively, of accreted dividends on preferred stock. The decrease in accreted dividends in 2003 from 2002 was the result of the August 2002 conversion of 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of our common stock using a conversion price of $12.54 per share. Included in the conversion was approximately $2.1 million in preferred stock dividends accrued in prior years. The increase in the net loss applicable to common stock was primarily a result of the increase in loss from operations, a non-cash loss on investments of $2.4 million related to the other-than-temporary impairment of our investments in ATL and Hybridon and the absence of a net gain on debt extinguishment recorded in 2002.

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, 2004, we have earned approximately $443.1 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 $593.2 million from the sale of equity securities. We have borrowed approximately $382.1 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2004, we had cash, cash equivalents and short-term investments of $103.9 million, working capital of $82.2 million and a stockholders' deficit of $72.1 million. In comparison, we had cash, cash equivalents and short-term investments of $215.5 million, working capital of $194.0 million and stockholders' equity of $67.2 million as of December 31, 2003. Our $100.0 million Lilly research collaboration loan, of which $95.0 million was outstanding as of December 31, 2004, is due in August 2005. We can repay this loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down

the remaining amount available under the loan, we could repay the loan for 2.5 million shares of our common stock. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation in the current quarter. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, to purchase property, plant, and equipment, pursue patents, and to pay our debt and capital lease obligations. In addition, we made a $10.0 million cash investment in Alnylam as part of our strategic alliance with them.

As of December 31, 2004, our debt and other obligations totaled $258.9 million, compared to $250.6 million at December 31, 2003. Our debt and other obligations at December 31, 2004 included current and long-term deferred contract revenue of approximately $11.8 million and other contractual obligations. The increase in our debt and other obligations was primarily due to additional draw downs from the $100.0 million interest-free loan from Lilly, which we discounted to their present value by imputing interest on the amounts at 20% and accreting to their face value over their term by recording interest expense. The increase in debt was partially offset by the repayment in January of convertible partner debt from Boehringer Ingleheim International BmbH, or BI, of approximately $6.4 million, the payment of principal and interest related to our standard operating debt, and payments related to our capital leases. We also financed $3.2 million in capital additions under our existing capital lease financing arrangement. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required to support our business.

We will continue to use lease financing as long as the terms remain commercially attractive. 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 through at least mid 2007. The following table summarizes our contractual obligations as of December 31, 2004. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Lilly Research Collaboration Loan	$ 95.0	$ 95.0	$ —	$ —	$ —
5 ½% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ 125.0	$ —
Standard Operating Debt	$ 32.2	$ 6.4	$ 18.8	$ 7.0	$ —
Capital Lease and Other Obligations	$ 6.7	$ 4.2	$ 2.3	$ 0.2	$ —
Operating Leases	$ 9.6	$ 2.8	$ 4.5	$ 1.9	$ 0.4

Our contractual obligations consist primarily of our publicly traded convertible debt and Lilly research collaboration loan. We can repay our Lilly research collaboration loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down the remaining amount available under the loan, we could repay the loan for 2.5 million shares of our common stock. In addition, we also have standard operating debt, capital leases and other obligations. Our standard operating debt includes a term loan from Silicon Valley Bank, and our mortgage loan payable to another bank.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to BI and Elan. 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, which was 5.25% at December 31, 2004. 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, of which $6.4 million plus accrued interest we paid in January 2004. The carrying value of the term loan at December 31, 2004 and 2003 was $26.1 million and $32.0 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, 2004 and 2003, the principal outstanding on the notes was $125.0 million.

In August 2001, Lilly made available to us a $100.0 million interest-free loan to fund the joint research collaboration between the two companies. The loan is interest-free and is repayable, at our option, in cash or common stock at $40 per share at the end of four years. The term of the loan provides for quarterly draw downs by us. As of December 31, 2004, we had drawn down $95.0 million of the $100.0 million available. We discounted the $95.0 million loan to its 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 are accreting 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 represents value given to us by Lilly to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance. As of December 31, 2004, the balance in long-term obligations was $83.2 million and the balance in deferred revenue was $11.8 million.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2004 for the purchase of services, capital equipment and materials as part of our normal course of business.

As part of our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology, we decided to close our research and development laboratory in Singapore during the first quarter of 2005 and terminate our agreement with the Singapore Economic Development Board, or EDB. To date, we have received $1.5 million in cash payments under our $8.0 million grant from the EDB and do not anticipate receiving any additional payments under the agreement.

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.

Prospective Information

Restructuring Activities

We expect to incur additional charges relating to restructuring activities during the first quarter of 2005, including those associated with employee termination costs, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore. We expect that our cost containment measures will significantly decrease our cash use in 2005 as compared to 2004.

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 has been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2004 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, 2004 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

There have been no significant changes in our internal controls or in other factors that could significantly affect our disclosure controls and procedures subsequent to the date of the previously mentioned evaluation.

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, 2004, 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, 2004.

Our management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2004 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 Shareholders 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, 2004, 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, 2004, 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, 2004, 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, 2004 and 2003 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, 2004, and our report dated March 3, 2005 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 3, 2005

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 April 11, 2005 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2004 Annual Meeting of stockholders to be held on May 26, 2005.

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, 2004.

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	3,863,000 (a)	$8.92	5,108,000 (c)
Equity compensation plans not approved by stockholders	4,804,000 (b)	$7.88	792,000
Total	8,667,000	$8.34	5,900,000

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

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

(c) Of these shares, 72,993 remained available for purchase under the 2000 Employee Stock Purchase Plan as of December 31, 2004. 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 nonstatutory 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, 2004, the 2000 Plan had 5,596,000 shares reserved for issuance, options to purchase an aggregate of 4,804,000 shares have been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 394,000 shares have been exercised under the 2000 Plan, and 792,000 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, 2004, approximately 4,804,000 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 51 through 55.

(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 15th day of March, 2005.

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 15, 2005
/S/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 15, 2005
/S/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 15, 2005
/S/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	March 15, 2005
/S/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 15, 2005
/S/ FREDERICK T. MUTO Frederick T. Muto	Director	March 15, 2005
/S/ JOHN C. REED, M.D., Ph.D. John C. Reed, M.D., Ph.D.	Director	March 15, 2005
/S/ MARK B. SKALETSKY Mark B. Skaletsky	Director	March 15, 2005
/S/ JOSEPH H. WENDER Joseph H. Wender	Director	March 15, 2005

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)
4.7	Form of Right Certificate.(17)
4.13	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)
4.14	Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.15	Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.16	Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.17	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)
4.18	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)
4.19	Form of 5 1/2% Convertible Subordinated Note due 2009.(16)
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)
10.9	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $6,000,000, together with the related Deed of Trust and Assignment of Rents dated March 24, 1997.(5)
10.10	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $3,706,620, together with the related Deed of Trust and Assignment of Rents dated March 24, 1997.(5)
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)

Exhibit Number	Description of Document
10.15	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.16	Development and License Agreement, dated August 14, 2001 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(20)
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)
10.29	Amended and Restated Collaboration Agreement dated June 17, 2002, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(27)
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 10b5-1 Trading Plan.(29)
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)
10.38	Waiver and Release Agreement dated June 5, 2003 between the Registrant and Eli Lilly and Company (with certain confidential information deleted). (32)
10.39	Amendment Number One to Development and License Agreement dated June 5, 2003 between the Registrant and Eli Lilly and Company (with certain confidential information deleted). (32)
10.41	Form of Severance Agreement dated April 2003 entered into between the Registrant and its executive officers and certain key employees, together with related schedule. (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)

Exhibit Number	Description of Document
10.44	Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement. (12)
10.45	Grant letter dated October 31, 2003 from the Singapore Economic Development Board to ISIS Pharmaceuticals Singapore Pte Ltd (with certain confidential information deleted) (12)
10.47	Subcontract No. 44076514 dated February 26, 2004 between Isis Pharmaceuticals, Inc. and Science Applications International Corporation (with certain confidential information deleted).(13)
10.48	Strategic Collaboration and License Agreement dated March 11, 2004 between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted). (18)
10.49	Investor Rights Agreement dated March 11, 2004 between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc. (23)
10.50	Securities Purchase Agreement dated June 4, 2004 between Isis Pharmaceuticals, Inc. and Elan Pharmaceutical Investments II, Ltd.(26)
10.51	Development Agreement dated September 30, 2004 between Isis Pharmaceuticals, Inc. and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted). (34)
10.52	Amendment No. 1 to License Agreement between Isis and Eyetech
10.53	Sale and Assignment Agreement between Isis and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted)
10.54	Security Agreement between Isis and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted)
10.55	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan
10.56	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan
10.57	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan
10.58	Collaboration and License Agreement between Isis and Sarissa, dated Feb 10, 2005
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.

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

ISIS PHARMACEUTICALS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF REGISTERED INDEPENDENT PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders
Isis Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2004 and 2003, 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, 2004. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated 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 consolidated financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the consolidated financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall consolidated financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc. at December 31, 2004 and 2003, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2004, 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 internal control over financial reporting as of December 31, 2004, 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 3, 2005 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 3, 2005

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

	December 31, 2004	December 31, 2003
ASSETS		
Current assets:		
Cash and cash equivalents	$ 27,250	$ 33,117
Short-term investments	76,633	182,387
Contracts receivable	10,048	2,657
Inventory	2,722	13,995
Other current assets	8,956	7,405
Total current assets	125,609	239,561
Property, plant and equipment, net	28,454	34,790
Licenses, net	26,104	28,363
Patents, net	19,097	22,374
Deposits and other assets	3,854	8,479
Investments in corporate securities	5,307	1,375
Total assets	$ 208,425	$ 334,942
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 6,967	$ 3,720
Accrued compensation	3,475	4,149
Accrued liabilities	8,238	6,527
Current portion of long-term obligations	10,546	16,477
Current portion of deferred contract revenue	14,190	14,684
Total current liabilities	43,416	45,557
5 ½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	111,611	88,397
Long-term deferred contract revenue, less current portion	531	8,810
Stockholders' equity (deficit):		
Series B Convertible Exchangeable 5% Preferred stock, $0.001 par value; 4,605 shares authorized, no shares issued or outstanding at December 31, 2004; 16,620 shares authorized, 12,015 shares issued and outstanding at December 31, 2003	—	12,015
Accretion of Series B Preferred stock dividends	—	2,560
Common stock, $0.001 par value; 100,000,000 shares authorized 57,447,333 and 55,557,253 shares issued and outstanding at December 31, 2004 and 2003, respectively	57	56
Additional paid-in capital	623,706	604,948
Deferred compensation	(72)	(294)
Accumulated other comprehensive income	2,623	3,476
Accumulated deficit	(698,447)	(555,583)
Total stockholders' equity (deficit)	(72,133)	67,178
Total liabilities and stockholders' equity (deficit)	$ 208,425	$ 334,942

See accompanying notes.

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

	Years Ended December 31,		
	2004	**2003**	**2002**
Revenue:			
Research and development revenue under collaborative agreements	$ 32,617	$ 49,467	$ 67,820
Research and development revenue from affiliates	—	—	11,942
Licensing and royalty revenue	10,007	523	417
Total revenue	42,624	49,990	80,179
Expenses:			
Research and development not including compensation (benefit) related to stock options of ($8), $673, and ($2,018) in 2004, 2003 and 2002, respectively	118,474	116,963	124,074
General and administrative not including compensation (benefit) related to stock options of $2, $240, and ($984) in 2004, 2003, and 2002, respectively	9,582	9,289	8,547
Compensation (benefit) related to stock options	(6)	913	(3,002)
Restructuring activities	32,427	1,803	1,373
Total operating expenses	160,477	128,968	130,992
Loss from operations:	(117,853)	(78,978)	(50,813)
Equity in loss of affiliates	—	—	(16,011)
Investment income	2,999	5,100	8,462
Interest expense	(22,592)	(18,680)	(16,562)
Loss on investment	(5,057)	(2,438)	—
Loss on prepayment of 14% Notes	—	—	(2,294)
Gain on prepayment of 12% Notes	—	—	4,976
Net loss	(142,503)	(94,996)	(72,242)
Accretion of dividends on preferred stock	(361)	(694)	(1,060)
Net loss applicable to common stock	$ (142,864)	$ (95,690)	$ (73,302)
Basic and diluted net loss per share	$ (2.52)	$ (1.73)	$ (1.35)
Shares used in computing basic and diluted net loss per share	56,642	55,463	54,480

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
Years Ended December 31, 2004, 2003 and 2002
(in thousands)

	Preferred stock			Common stock						
Description	Shares	Amount	Dividend Accretion	Shares	Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2001	132	$24,030	$ 2,933	53,750	$ 54	$582,258	$ (245)	$ 660	$ (386,591)	$ 223,099
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(73,302)	(73,302)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(1,268)	—	(1,268)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(74,570)
Dividends accrued on preferred stock	—	—	1,060	—	—	—	—	—	—	1,060
Deferred compensation	—	—	—	—	—	(3,188)	3,188	—	—	—
Options exercised and employee stock purchase plan	—	—	—	683	1	5,139	—	—	—	5,140
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(3,002)	—	—	(3,002)
Issuance of common stock	—	—	—	126	—	3,750	—	—	—	3,750
Conversion of preferred stock into common stock	(120)	(12,015)	(2,127)	657	—	14,142	—	—	—	—
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 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)

See accompanying notes.

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

	Years Ended December 31,		
	2004	2003	2002
Operating activities:			
Net loss	$ (142,503)	$ (94,996)	$ (72,242)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	8,401	8,551	5,985
Amortization of patents	1,442	1,217	927
Amortization of licenses	2,327	2,485	2,512
Compensation (benefit) related to stock options	(6)	913	(3,002)
Deferred interest on long-term debt	13,049	5,369	8,634
Loss on prepayment of 14% notes	—	—	2,294
Gain on prepayment of 12% notes	—	—	(4,976)
Accrued interest on prepayment of debt	—	—	(34,706)
Equity in losses of affiliates	—	—	16,011
Loss on investments	5,057	2,438	—
Restructuring activities	32,427	—	—
Non-cash expenses related to patents and fixed assets	2,275	2,813	1,622
Gain on disposal of property, plant and equipment	—	—	(260)
Changes in operating assets and liabilities:			
Contract receivable	(7,391)	12,249	(4,546)
Inventory	(9,699)	(2,905)	(11,090)
Other current and long-term assets	1,373	962	7,106
Accounts payable	3,247	(1,804)	(2,147)
Accrued compensation	(674)	819	(2,316)
Accrued liabilities	1,711	(267)	2,812
Deferred contract revenues	(12,787)	(33,318)	(6,999)
Net cash used in operating activities	(101,751)	(95,474)	(94,381)
Investing activities:			
Purchase of short-term investments	(72,479)	(152,910)	(200,563)
Proceeds from the sale of short-term investments	176,147	156,943	196,075
Purchases of property, plant and equipment	(3,526)	(7,554)	(36,834)
Licenses and other assets	(6,411)	(6,404)	(9,536)
Strategic investments	(10,000)	—	—
Investments in affiliates	—	(5,193)	(9,511)
Net cash provided by (used in) investing activities	83,731	(15,118)	(60,369)
Financing activities:			
Net proceeds from issuance of equity	4,051	1,700	8,890
Proceeds from 5 1/2% convertible subordinated notes	—	—	125,000
Proceeds from long-term borrowing	24,470	67,049	52,334
Principal payments on prepayment of debt	—	—	(52,704)
Principal payments on debt and capital lease obligations	(16,368)	(26,896)	(3,925)
Net cash provided by financing activities	12,153	41,853	129,595
Net increase (decrease) in cash and cash equivalents	(5,867)	(68,739)	(25,155)
Cash and cash equivalents at beginning of year	33,117	101,856	127,011
Cash and cash equivalents at end of year	$ 27,250	$ 33,117	$ 101,856
Supplemental disclosures of cash flow information			
Interest paid	$ 8,990	$ 12,778	$ 39,333
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt for licensing costs	$ —	$ —	$ 1,050
Additions to deposits and other assets from sale of equipment	$ —	$ —	$ 300
Additions to other current assets from sale of equipment	$ —	$ —	$ 160
Additions to long-term investment for acquired corporate securities	$ —	$ 750	$ —
Conversion of preferred stock into common stock	$ 14,934	$ —	$ 14,142
Decrease in inventory and deferred revenue	$ —	$ 8,750	$ —
Decrease in property plant and equipment and notes payable	$ —	$ 21,200	$ —

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("the Company") and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Hepasense, Ltd. ("Hepasense"), and Orasense, Ltd ("Orasense"). There were no current operations or results of operations for Hepasense, Ltd. or Orasense, Ltd for the year ended December 31, 2004. As more fully described in *Note 8 -- Restructuring Activities,* the Company decided to close 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 15.2 million at December 31, 2004 consisted of shares issuable upon exercise of stock options and convertible debt. As Isis incurred a loss in the years ended December 31, 2004, 2003 and 2002, 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, 2004, 2003 and 2002, research and development costs of approximately $36.3 million, $30.2 million and $68.3 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.

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 records revenue from federal research grants during the period in which it incurs 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. As of December 31, 2004, Isis had drawn down $95.0 million on the $100.0 million loan. Isis discounted the $95.0 million loan to its 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 accretes 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 represents value Lilly gave to Isis to help fund the research collaboration. Isis accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Research and development revenue from affiliates

In late 2002, Isis terminated its HepaSense and Orasense collaborations with Elan Corporation plc ("Elan") and as a result, Isis no longer earns revenue from these collaborations.

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.

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 established 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 quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income and these amounts have not been material. 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 Pharmaceuticals, Inc ("Alnylam"), compared to a non-cash loss on investments of $2.4 million in 2003 related to the impairment of investments in Antisense Therapeutics Limited ("ATL") and Hybridon, Inc. ("Hybridon"). The 2004 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.

Inventory valuation

Isis' inventory includes drugs with alternative uses that are used primarily for its clinical development activities and drug products it manufactures for its partners under contractual terms. Isis states its inventory at the lower of cost or market, with cost determined 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. In the second quarter of 2003, Isis reduced the carrying value of its raw materials related to Affinitak to zero. In the fourth quarter of 2004, Isis reduced the carrying value of its inventory by $21.0 million (*Note 8 -- Restructuring Activities).*

Inventory includes the following categories as of December 31, 2004 and 2003 (net realizable value in thousands):

	December 31,	
	2004	2003
Raw materials	$ 1,329	$ 1,526
Work in process	—	9,920
Finished goods	1,393	2,549
	$ 2,722	$ 13,995

Property, plant and equipment

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

	December 31,	
	2004	2003
Land	$ 1,163	$ 1,163
Buildings and improvements	30,305	29,859
Equipment and computer software	27,234	49,108
Furniture and fixtures	1,959	3,356
	60,661	83,486
Less accumulated depreciation	(32,207)	(48,696)
	$ 28,454	$ 34,790

During 2003, Isis reduced to zero approximately $21.2 million in buildings, building improvements and equipment related to the debt repayment waiver Lilly granted Isis for amounts Lilly loaned Isis to fund the construction of a new manufacturing suite dedicated to the commercial production of Affinitak. *(Note 6—Collaborative Arrangements and Licensing Agreements).* In the fourth quarter of 2004, Isis recorded a net write-down of $1.2 million for excess or idle property and equipment, consisting of $2.9 million less accumulated deprecation of $1.7 million. *(Note 8 -- Restructuring Activities).*

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 cost related to exclusive licenses. Isis' license from Hybridon comprises the majority of the license balance as of December 31, 2004, 2003 and 2002. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between nine years and 15 years. Accumulated amortization related to licenses was $9.8 million and $7.5 million at December 31, 2004 and 2003, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2005, 2006, 2007, 2008 and 2009.

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 6.1 years and 6.5 years at December 31, 2004 and 2003, respectively. In the fourth quarter of 2004, Isis recorded a non-cash charge of $6.1 million 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 $5.4 million and $4.4 million at December 31, 2004 and 2003, respectively. Based on existing patents, estimated amortization expense related to patents is as follows (in thousands):

Years Ending December 31,	Amortization (in thousands)
2005	$1,362
2006	$1,318
2007	$1,184
2008	$1,062
2009	$ 966

Investment in affiliates

Isis uses the equity method of accounting to account for its investments in 50% or less owned companies over which it has the ability to exercise significant influence. Isis also accounted for investments in its joint ventures, Orasense and HepaSense, using the equity method of accounting. At December 31, 2003, Isis had the following investments accounted for using the equity method:

Orasense and HepaSense

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. While Isis owned 80.1% of the outstanding common stock of Orasense and HepaSense, throughout the respective terms of the collaborations related to the joint ventures, Elan and its subsidiaries retained significant minority investor rights that were considered "participating rights" as defined in EITF 96-16. Accordingly, Isis accounted for its investment in each joint venture under the equity method of accounting for the year ended December 31, 2002. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. In June 2004, Isis entered into an agreement with a subsidiary of Elan to acquire Elan's minority interest in Orasense and HepaSense. As a result, Isis owned 100% of Orasense and HepaSense at December 31, 2004 (*Note 6—Collaborative Arrangements and Licensing Agreements).*

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*. For the year ended December 31, 2002, Isis recorded an impairment charge of $605,000 for the write-down of intellectual property related to the restructuring of the GeneTrove program. In the fourth quarter of 2004, Isis recorded a charge of $11.5 million 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, 2004, Isis had a collaborative arrangement with Ercole Biotech, Inc. ("Ercole"), a development stage biopharmaceutical company developing drugs based on RNA splicing technology. Isis considers Ercole to be a Variable Interest Entity ("VIE") under the provisions of FIN No. 46. Pursuant to the terms of a Note and Warrant Purchase Agreement (the "Agreement"), during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000 respectively, in exchange for a convertible promissory note (the "Note"). Isis expensed the payments when made. The Note is secured by all of Ercole's assets, including intellectual property and licenses, and will convert into securities that Ercole issues in a qualified financing, as defined by the Agreement. Isis is not required to consolidate Ercole's results of operations under FIN No. 46.

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 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 the statement of operations. Variable stock options can result in significant increases and decreases in compensation expense, subject to the variability of Isis' stock price. As of December 31, 2002, optionholders had exchanged all of these options, or the options had expired. As of December 31, 2004 all of the exchanged, unexpired options were fully vested.

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program") to maintain one of Isis' key assets, its employee base, in a manner that was sensitive to shareholder interests. 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 $8,000 in 2004 and non-cash compensation expense of approximately $886,000 in 2003 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 with compensation expense related to non-employee options of $2,000 and $27,000 for 2004 and 2003, 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 primarily for compensation expense 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").

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

	2004	2003	2002
Net loss applicable to common stock—as reported	$ (142,864)	$ (95,690)	$ (73,302)
Net loss applicable to common stock—pro forma	$ (150,045)	$ (101,099)	$ (95,329)
Basic and diluted net loss per share—as reported	$ (2.52)	$ (1.73)	$ (1.35)
Basic and diluted net loss per share—pro forma	$ (2.65)	$ (1.82)	$ (1.75)

For purposes of proforma 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		
	2004	2003	2002	2004	2003	2002
Risk free interest rate	4.2%	4.3%	3.8%	4.2%	4.3%	3.8%
Dividend yield	0%	0%	0%	0%	0%	0%
Volatility	62.4%	69.5%	78.7%	57.2%	49.5%	80.9%
Expected Life	6.4 years	6.2 years	5.4 years	6 months	6 months	6 months

The weighted average fair value of options granted was $6.58 for 2004, $5.70 for 2003, and $11.34 for 2002. The weighted average fair value of the ESPP purchase rights was $4.67, $4.46, and $5.60 for 2004, 2003 and 2002, respectively.

Comprehensive income (loss)

SFAS 130, *Reporting Comprehensive Income* ("SFAS 130") requires Isis to display comprehensive income (loss) and its components as part of Isis' full set of consolidated financial statements. The measurement and presentation of net income (loss) did not change. Comprehensive income (loss) is comprised of net income (loss) and certain changes in equity that are excluded from net income (loss). Specifically, SFAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which Isis reported separately in stockholders' equity, to be included in accumulated other comprehensive income (loss). Comprehensive income (loss) for the years ended December 31, 2004, 2003 and 2002 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 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

On December 16, 2004, the Financial Accounting Standards Board ("FASB") issued SFAS 123(R), *Share-Based Payment* ("SFAS 123(R)"), which is a revision of SFAS 123. Generally, the approach in SFAS 123(R) is similar to the approach described in SFAS 123. However, SFAS 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values. Pro forma disclosure is no longer an alternative. This statement also eliminates the ability to account for share-based compensation transactions using APB Opinion No. 25. The statement is effective at the beginning of the first interim period beginning after June 15, 2005. Early adoption will be permitted in periods in which financial statements have not yet been issued. Isis expects to adopt SFAS 123(R) on July 1, 2005.

SFAS 123(R) permits public companies to adopt its requirements using one of two methods: 1) A "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS 123 for all awards granted to employees prior to the effective date of SFAS 123(R) that remain unvested on the effective date, 2) A "modified retrospective" method which includes the requirements of the modified prospective method described above, but also permits entities to restate based on the amounts previously recognized under SFAS 123 for purposes of pro forma disclosures either (a) all prior periods presented or (b) prior interim periods of the year of adoption. Isis plans to adopt SFAS 123 no later than July 1, 2005, but has not yet determined what method it will use.

As permitted by SFAS 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 SFAS 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. The impact of adoption of SFAS 123(R) cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had Isis adopted SFAS 123(R) in prior periods, the impact of that standard would have approximated the impact of SFAS 123 as described in the disclosure of pro forma net income and earnings per share in Note 1 to the consolidated financial statements. SFAS 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* ("SFAS 151"), 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.

In March 2004, the FASB issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF 03-1, which was originally effective for interim and annual reporting periods beginning after June 15, 2004 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. Isis does not expect that the adoption of EITF 03-1 will have a material impact on its operating results and financial position.

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, 2004:

Less than 1 year	55%
1 - 3 years	39%
3 - 5 years	6%
Total	100%

Isis has an ownership interest of less than 20% each in three 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 include Alnylam, ATL and Hybridon, which are publicly-traded, and Santaris Pharma A/S ("Santaris") and OncoGenex Technologies, Inc. ("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 2004 and 2003.

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

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
Equity securities	—	8,367	3,282	(129)	11,520
Total long-term investments		43,251	3,282	(440)	46,093
		$ 85,530	$ 3,282	$ (659)	$ 88,153

December 31, 2003	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. corporate debt securities	1 or less	$ 40,112	$ 147	$ (6)	$ 40,253
U.S. Treasury securities and obligations of U.S. government agencies	1 or less	26,286	116	—	26,402
Total short-term investments		66,398	263	(6)	66,655
U.S. corporate debt securities	1 to 2	50,793	487	(16)	51,264
U.S. Treasury securities and obligations of U.S. government agencies	1 to 5	64,442	173	(147)	64,468
Equity securities	—	3,424	2,722	—	6,146
Total long-term investments		118,659	3,382	(163)	121,878
		$ 185,057	$ 3,645	$ (169)	$ 188,533

Investments considered to be temporarily impaired at December 31, 2004 are as follows:

		Less than 12 Months of temporary impairment		Greater than 12 Months of temporary impairment		Total temporary impairment	
	Number of Investments	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
U.S. corporate debt securities	29	$ 31,922	$ (168)	$ —	—	31,922	(168)
U.S. Treasury securities and obligations of U.S. government agencies	29	26,714	(205)	14,408	(157)	41,122	(362)
Total Debt Securities	58	58,636	(373)	14,408	(157)	73,044	(530)
Equity securities	1	474	(129)	—	—	474	(129)
Total temporarily impaired securities	59	$ 59,110	$ (502)	$ 14,408	(157)	73,518	(659)

Isis believes that the decline in value 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 or sooner in the event of a change in the market interest rate environment.

3. Long-Term Obligations and Commitments

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

	December 31, 2004	December 31, 2003
Convertible partner debt		
Eli Lilly	$ 95,000	$ 73,750
Boehringer Ingleheim	—	6,376
Total convertible partner debt	$ 95,000	$ 80,126
Standard operating debt	32,181	38,392
5 ½% convertible subordinated notes	125,000	125,000
Capital leases and other obligations	6,741	7,116
Total	$ 258,922	$ 250,634
Less: current portion	(10,546)	(16,477)
Less: Eli Lilly debt classified as deferred revenue	(11,765)	(20,760)
Total Long-Term Obligations	$ 236,611	$ 213,397

Convertible Partner Debt

Lilly

In August 2001, Lilly made available to Isis a $100.0 million loan facility to fund joint research between the two companies. The loan is interest-free and payable, at Isis' option, in cash or common stock at $40 per share in August 2005. The loan facility provides for quarterly draw-downs by Isis in varying amounts. As of December 31, 2004 and 2003, Isis had drawn down $95.0 million and $73.8 million, respectively. Isis accounts 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 carries the net present value of the draw-downs as a long-term obligation and records interest expense over the term of the loan. The difference between the cash received and the present value of the loan represents value Lilly gave Isis to help fund the research collaboration. Isis accounts for this difference as deferred revenue and recognizes it as research and development revenue under collaborative agreements over the period of performance. At December 31, 2004 and 2003, the balance in long-term obligations related to this loan was $83.2 million and $53.0 million, respectively, and the balance in deferred revenue was $11.8 million and $20.8 million, respectively. Isis can repay this loan at its option in either cash or our common stock at a fixed conversion price of $40 per share. If Isis draws down the remaining amount available under the loan, it could repay the loan for 2.5

million shares of Isis common stock. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation on the accompanying consolidated balance sheet.

Elan

During 1999 and 2000, in conjunction with the HepaSense and Orasense joint ventures, Elan made available to Isis credit facilities of up to $30.4 million, evidenced by convertible promissory notes. The terms of these notes provided for interest at 12% annually, with maturities through January 2006. The notes were convertible into the common stock of Isis at any time by either party, as defined by the underlying agreements. In July 2002, Isis prepaid $19.7 million of the then-outstanding debt with $14.7 million in cash, resulting in a gain of approximately $5.0 million for the year ended December 31, 2002. As of December 31, 2002, there was $7.2 million outstanding under the Orasense credit facility. Isis paid these borrowings in full from the proceeds of the Company's term loan with Silicon Valley Bank in December 2003. Isis can no longer borrow funds against these credit facilities.

Boehringer Ingelheim

During 1997 and 1996, Isis borrowed a total of $22.6 million under a $40.0 million line of credit made available pursuant to the terms of its collaborative agreement with Boehringer Ingelheim ("BI"). Borrowings under the line of credit bore interest at the seven year United States interbanking rate plus 2.0%, determined at the time each advance was made, and ranged from 8.36% to 8.46%. Principal borrowings were repayable in cash or Isis common stock, at the option of Isis. In October 2003, Isis repaid, in cash, the first installment of $8.3 million, plus interest. Isis repaid the remaining principal installments of $7.9 million, plus interest, and $6.4 million, plus interest, in December 2003 and January 2004, respectively, using the proceeds of the Company's term loan with Silicon Valley Bank.

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 (5.25% at December 31, 2004), 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, 2004 and 2003. Isis used the proceeds of the loan to pay off the Elan and BI partner debt in late 2003 and early 2004. The carrying value of this loan at December 31, 2004 and 2003 was $26.1 million and $32.0 million, respectively, which approximated fair value.

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. The loan is secured by Isis' real property and bears interest at the prime rate plus 0.5% (5.75% at December 31, 2004), is payable in monthly payments of principal and interest, with the final principal payment due on December 2006. Isis borrowed its final installment of $998,000 on this loan in January 2003. The carrying value of this loan at December 31, 2004 and 2003 was $6.1 million and $6.4 million respectively, which approximated fair value.

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 December 31, 2004 and 2003, 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 $104.9 million and $101.2 million as of December 31, 2004 and 2003, respectively. Isis did not include these convertible notes in the computation of diluted net loss per share because the effect would be anti-dilutive.

Isis used a portion of the net proceeds from the convertible notes to prepay amounts outstanding on its 14% Senior Subordinated Notes, and certain obligations under its credit facilities with Elan. These early debt retirements resulted in a $2.3 million loss on prepayment of 14% Notes and a $5.0 million gain on prepayment of 12% Notes, and are included as such on the accompanying Consolidated Statements of Operations for the year ended December 31, 2002.

Capital Leases and Other Obligations

At December 31, 2004 and 2003, Isis had approximately $5.8 million and $6.3 million outstanding, respectively, under various capital equipment leases which bear interest at rates ranging from 5.64% to 9.82% and mature at various dates through 2008. At December 31, 2004 and 2003, Isis had approximately $900,000 and $860,000, respectively, under various contractual obligations, of which $700;000 represented amounts due to Integrated DNA Technologies, Inc. ("IDT") as part of the supply agreement entered into in December 2001 *(Note 6—Collaborative Arrangements and Licensing Agreements)*.

Annual debt and other obligation maturities at December 31, 2004 are as follows (in thousands):

2005	$	105,546
2006		13,533
2007		7,555
2008		7,288
2009		125,000
Total	$	258,922

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through May 2010. Two of the building leases have two extension options for five years each. Annual future minimum payments under capital and operating leases as of December 31, 2004 are as follows (in thousands):

	Operating Leases	Capital Leases
2005	$ 2,759	$ 3,735
2006	2,802	1,571
2007	1,705	869
2008	993	190
2009	920	—
Thereafter	391	—
Total minimum payments	$ 9,570	$ 6,365
Less amount representing interest		(524)
Present value of future minimum payments		$ 5,841
Less current portion		(3,408)
Long-term portion		$ 2,433

Rent expense for the years ended December 31, 2004, 2003, and 2002 was $3.1 million, $3.2 million, and $2.9 million, respectively. Cost of equipment under capital leases at December 31, 2004 and 2003 was $23.9 million and $20.7 million, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2004 and 2003 was approximately $16.9 million and $13.6 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, 2004, there were no Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible Exchangeable 5% Preferred Stock shares issued or 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 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 (the "Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right (a "Right") for each outstanding share of Isis common stock, par value $0.001 per share (the "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 (other than the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share (the "Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share (the "Purchase Price"), subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and the qualifications, limitations and restrictions which make its value approximately equal to the value of a Common Share. Under certain conditions, Isis' Board of Directors may redeem the Rights in whole, but not in part, at a price of $0.001 per Right.

Common Stock

At December 31, 2004 and 2003, Isis had 100,000,000 shares of common stock authorized, of which 57,451,671 and 55,557,253 were issued and outstanding, respectively. As of December 31, 2004, total common shares reserved for future issuance was approximately 14,573,000.

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 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, 2004, a total of 3,514,000 options were outstanding, options to purchase 2,007,000 shares were exercisable, and 4,640,000 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 optionee's employment or service as a consultant, employee or director. At December 31, 2004, a total of 4,804,000 options were outstanding, 3,086,000 shares were exercisable, and 792,000 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, 2004, approximately 4,804,000 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 plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 803,000 shares of common stock reserved 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, 2004, a total of 349,000 options were outstanding, 166,000 of the shares issued under this plan were exercisable and 395,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 2002 through December 31, 2004 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
Outstanding at December 31, 2001	8,220	$3.75 to $26.65	$ 9.88
Granted	2,197	$6.87 to $22.19	
Exercised	(505)	$4.00 to $17.88	
Terminated	(656)	$5.38 to $24.17	
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

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 12/31/04	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/04	Weighted Average Exercise Price
$3.12 - $4.98	234	7.73	$4.18	68	$4.05
$4.76 - $7.52	5,280	6.65	$6.32	2,594	$6.38
$7.22 - $10.82	1,550	6.47	$9.31	1,194	$9.55
$10.88 - $16.30	1,148	4.39	$12.86	1,065	$12.85
$16.35 - $18.70	228	6.10	$17.36	169	$17.43
$21.05 - $26.65	227	6.97	$21.19	169	$21.19
	8,667			5,259	

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 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 2004, 327,145 shares were issued under this plan to employees at prices ranging from $4.47 to $4.86 per share. At December 31, 2004, 72,993 shares were available for purchase under this plan.

Warrants

In June 2004, Isis entered into an agreement with a subsidiary of Elan to acquire Elan's minority interest in Orasense and HepaSense. In connection with this agreement, Isis cancelled a warrant Elan held to purchase 14,881 shares of Isis common stock that was issued in 2000 as part of the joint venture collaboration between Isis and Elan to form HepaSense.

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, 2004, this warrant remained outstanding at an exercise price of $59.48 per share. The warrant expires April 25, 2007.

In 1999, Isis issued a warrant to purchase 215,000 shares of common stock to Elan as part of the joint venture collaboration between Isis and Elan to form Orasense. The warrant expired unexercised on April 19, 2004.

In 1997 and 1998, Isis issued warrants to purchase 500,000 and 300,000 shares of common stock, respectively, in conjunction with a private debt financing agreement. The warrants expired unexercised on November 1, 2004 (*Note 3 -- Long-Term Obligations and Commitments).*

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2004 and 2003 are shown below (in thousands). Isis recognized valuation allowances of $283.7 million and $235.0 million for 2004 and 2003, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2004	2003
Deferred tax assets:		
Capitalized research expense	$ 43,132	$ 86,827
Net operating loss carryforwards	189,148	110,652
Research and development credits	33,966	30,095
Deferred revenue	5,998	9,573
Accrued restructuring	13,335	—
Other, net	7,525	5,180
Total deferred tax assets	293,104	242,327
Deferred tax liabilities:		
Intangible Assets	(9,393)	(7,361)
Total deferred tax liabilities	(9,393)	(7,361)
Total net deferred tax assets	283,711	234,966
Valuation allowance for deferred tax assets	(283,711)	(234,966)
Net deferred tax assets	$ —	$ —

At December 31, 2004, approximately $7.1 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, 2004, Isis had federal, foreign and California tax net operating loss carryforwards of approximately $517.1 million, $530,000 and $140.4 million, respectively. Isis also had federal and California research credit carryforwards of approximately $23.5 million and $10.0 million, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of California loss carryforwards. The federal tax loss carryforwards and the research credit carryforwards will begin expiring in 2007 and 2005, respectively, unless previously 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 will begin expiring in 2005, 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

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly, including four key components:

First, Lilly purchased $75.0 million of Isis common stock at $18 per share.

Second, Isis licensed to Lilly rights to Affinitak, which was being tested in a Phase III trial for the treatment of non-small cell lung cancer, and which Lilly has decided to discontinue funding. Lilly paid Isis $25.0 million in up-front fees for Affinitak and reimbursed Isis for Isis' Affinitak development costs. During 2003 and 2002, Isis earned revenue of $11.1 million and $31.9 million, respectively, related to the reimbursement of Affinitak costs. Isis earned no revenue related to Affinitak during 2004.

Third, Isis initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related gene functionalization and target validation collaboration to determine the function of up to 1,000 genes. Key achievements and developments under this collaboration include:

- In 2002, Lilly and Isis expanded this collaboration to include oncology and the license of LY2181308, our antisense inhibitor of survivin for which we earned a $1.1 million license fee.

- In April 2003, Isis earned a $1.5 million milestone from Lilly in the development of LY2181308, the antisense inhibitor of survivin, as part of the research collaboration oncology expansion. LY2181308 is the first compound from the partnership selected by Lilly for clinical development. In November 2004, Lilly initiated Phase I clinical trials of LY218308 in cancer patients, marking a significant milestone in the partnership and triggering a $1.5 million milestone payment from Lilly to Isis. Isis' collaboration with Lilly also may generate additional milestone payments aggregating up to $25.0 million based on LY2181308 achieving specified regulatory and commercial milestones.

- In July 2003, Isis expanded the cancer research component of its antisense drug discovery collaboration with Lilly to include multiple antisense mechanisms, such as RNAi and alternative splicing, as well as third generation antisense chemistries. We are currently jointly developing antisense drugs with Lilly that work through an RNAi mechanism or use our chemistries as potential follow-on drugs to LY2181308.

- In May 2004, Lilly and Isis announced the extension of our antisense drug discovery collaboration in cancer. During this extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using second and third generation chemistries. An important component of this extension will be the exploration of potential new anti-cancer drug targets using RNA-directed technologies.

- In September 2004, Lilly licensed from Isis LY2275796. This second-generation antisense anti-cancer drug candidate targets eIF-4E. Isis earned a $750,000 payment from Lilly for the license. LY2275796 is the second compound from the partnership to be selected by Lilly for clinical development. Isis' collaboration with Lilly also may generate additional milestone payments aggregating up to $20.3 million based on LY2275796 achieving specified regulatory and commercial milestones.

Fourth, Lilly committed to lend Isis, interest-free, up to $100.0 million over a four-year period to fund its obligations under the drug discovery collaboration. Isis can repay this loan at its option in either cash or Isis common stock, at a fixed conversion price of $40 per share. During 2004, 2003 and 2002, Isis recorded revenue related to the research collaboration loan of $13.0 million, $7.5 million, and $3.2 million, respectively and corresponding interest expense during 2004, 2003, and 2002, of $13.0 million, $7.5 million, and $3.2 million, respectively.

Subsequent to August 2001, Isis and Lilly entered into additional agreements under the collaboration, as follows:

- In September 2002, Isis and Lilly entered into a supply agreement under which Isis agreed to manufacture Affinitak active pharmaceutical ingredient ("API") for Lilly. The agreement called for Lilly to pay Isis $8.75 million in cash for Affinitak raw materials that Isis would need to manufacture the API. Isis accounted for the $8.75 million as deferred revenue, and expected to recognize this balance into revenue as it shipped Affinitak API to Lilly. Neither Isis nor Lilly expected to realize a margin from this transaction.
- In addition, in September 2002, Isis entered into a manufacturing loan agreement with Lilly. Under the terms of the loan agreement, Lilly loaned to Isis $21.2 million to build a new commercial scale manufacturing facility for Affinitak. During the period of May 2002 through March 2003, Isis completed construction of the manufacturing suite and, as a result, incurred $21.2 million in construction costs which Isis reflected as property, plant and equipment on its balance sheet as of December 31, 2002. Neither Isis nor Lilly expected to realize a margin from this transaction.
- In March 2003, after Isis announced disappointing results from its Phase III trial of Affinitak, Isis and Lilly reached a mutually beneficial renegotiation of their manufacturing relationship, pursuant to which Lilly allowed Isis to keep the $8.75 million of raw materials. Lilly also waived repayment of the $21.2 million manufacturing loan it provided to Isis to build the manufacturing facility.

  Isis determined the estimated net realizable value of the Affinitak API should be written down to zero because: (i) Isis was moving away from first-generation drugs like Affinitak in favor of second-generation drugs, rendering most of the raw materials obsolete; and, (ii) Isis already had sufficient inventory of raw materials to manufacture its second-generation drugs for the then foreseeable future. Isis also determined there was no anticipated use of the manufacturing facility in the then-foreseeable future because Isis did not have a drug that required a large-scale commercial manufacturing facility and the long term prospects for utilization of the facility were unknown. Since these write-offs were triggered by one event and there was no impact to the statement of operations, Isis wrote-off the $8.75 million of deferred revenue against the related raw material inventory and the $21.2 million of long-term debt against the related fixed assets.

Antisense Drug Discovery Collaborations

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 Severe Acute Respiratory Syndrome, or 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. Isis earned no revenue from the grant in 2003.

As part of a strategic decision to reorganize and refocus the Company's resources to advance its most promising second-generation drugs and to continue the development of antisense technology, 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. To date, Isis has 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.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes of Taiwan ("ITRI") to identify antisense candidates targeting the coronavirus associated with 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 up-front 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 under this collaboration. This collaboration has ended in accordance with its terms.

Amgen

In December 2001, Isis entered into a three-year collaboration with Amgen, Inc. ("Amgen") to discover new antisense drugs. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration. Under the terms of the agreement, Isis is 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 and 2003, Isis earned revenue of $783,000 and $1.9 million, respectively, 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.

Merck & Co., Inc.

In May 2001, Isis licensed to Merck & Co, Inc. ("Merck"), Isis' preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. In exchange for the license, Isis received an upfront payment. In addition, Isis received development funding and earned a development milestone. During 2002, Isis earned revenue of $840,000 under this agreement. Isis reacquired full product rights to ISIS 113715 from Merck in December 2002. As a result, no revenue was earned for the years ended December 31, 2004 and 2003.

In June 1998, Isis entered into a research collaboration with Merck to discover small molecule drug candidates to treat patients infected with HCV. The collaboration, which concluded in May 2003 in accordance with its terms, provided that Merck would pay Isis' annual research support and milestone payments. Within the collaboration, Isis and Merck designed, synthesized, and evaluated novel compounds that Merck screened in its proprietary assays for identifying HCV replication inhibitors. Merck had the right to commercialize any drugs from the collaboration, and Isis retains the right to use technology developed in the collaboration in its antisense program. During 2003, and 2002, Isis earned revenue of $900,000 and $2.2 million, respectively, from Merck under the terms of this agreement. Isis earned no revenue for the year ended December 31, 2004.

Satellite Company Collaborations

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, "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.

Under the terms of the agreement, in exchange for the exclusive, worldwide license to the TS antisense drug, Sarissa issued to Isis a $1.0 million debt instrument (the "Sarissa Note"), which will convert into Sarissa's common stock upon its successful completion of a venture capital financing. Isis has not yet determined a value for the Sarissa Note. Under the agreement, Sarissa agreed to pay Isis milestone payments totaling up to $5.5 million for key clinical and regulatory achievements and royalties on any product sales. Sarissa is solely responsible for preclinical and clinical development of the drug.

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 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 of these drugs, the potential milestone payments total $3.4 million and are payable 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 of these drugs, the potential milestone payments total $3.4 million and are payable upon the occurrence of specified development and regulatory events. As of December 31, 2004, 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.

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, 2004 includes a short-term investment at fair market value of approximately $2.0 million and a long-term investment at fair market value of $3.9 million.

During 2004, Isis generated revenue from its relationship with Alnylam totaling $5.5 million, or 13%, of total revenue.

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 convertible debt, 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 promissory note ("the 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.

Antisense Therapeutics Ltd., Inc.

In December 2001, Isis licensed its compound, ATL 1102, formerly Isis 107248, to ATL, a publicly-traded company listed on the Australian Stock Exchange. Isis and ATL are participating in a five-year antisense drug discovery and development collaboration, under which ATL pays Isis research fees and reimbursed Isis for costs related to preclinical work on ATL 1102. ATL has the option to license additional drugs from Isis. 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, 2004, 2003 and 2002, Isis recorded revenue of $1.4 million, $811,000 and $3.7 million respectively, related to this collaboration. As of December 31, 2004, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was approximately 11%. Isis' balance sheets at December 31, 2004 and 2003 include a short-term investment at fair market value of $3.8 million and $3.6 million, respectively, related to this equity investment.

OncoGenex Technologies, Inc.

Pursuant to a November 2001 drug development collaboration, Isis agreed to co-develop and commercialize the anti-cancer antisense drug candidate, OGX-011, or ISIS 112989, with OncoGenex, a privately-held Canadian oncology-focused research and development company. Pursuant to the agreement, Isis shares in the costs of developing OGX-011. In exchange, Isis shares in any revenue generated by OncoGenex for OGX-011. In a September 2003 drug development collaboration, Isis also agreed to license certain technology and collaborate on the initial development of a second anti-cancer antisense drug candidate, OGX-225, a second-generation drug, with OncoGenex. Under the terms of the collaboration, during 2003 OncoGenex paid Isis an up-front fee and Isis acquired an ownership interest in OncoGenex of less than 10%. In addition, OncoGenex agreed to provide to Isis milestone payments totaling up to $3.5 million for key clinical and regulatory achievements and royalties on product sales. As of December 31, 2004, OncoGenex had not triggered any of these milestone payments related to OGX-225.

For the years ended December 31, 2004 and 2003, Isis earned revenue of $669,000 and $750,000, respectively, related to its collaboration with OncoGenex. Isis earned no revenue from OncoGenex during 2002. Isis' balance sheets at December 31, 2004 and 2003 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 has continuing obligations. Isis expects to recognize the $1.6 million in revenue and related costs of $1.4 million during the first quarter of 2005.

In January 2005, Isis broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drug candidates. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drug. OncoGenex agreed to pay Isis an upfront fee, milestone payments for key clinical and regulatory achievements, and royalties on future product sales.

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 is restricted 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 common stock. In May 2003, Pantheco A/S and Cureon A/S merged to form Santaris Pharma A/S. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of antidilution provisions related to Pantheco's stock. After the merger and as of December 31, 2004 and 2003, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheets at December 31, 2004 and 2003 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.

Antisense Commercialization Collaboration

Novartis Ophthalmics AG

In July 1997, Isis and Novartis Ophthalmics AG, ("Novartis"), formerly CIBA Vision Corporation, entered into an agreement granting Novartis exclusive worldwide distribution rights for Vitravene. Under the terms of the agreement, Isis is responsible for manufacturing Vitravene and Novartis is responsible for worldwide sales and marketing. Due to the low incidence of CMV retinitis among patients with AIDS, Novartis AG currently offers Vitravene on a limited basis. During 2002, Isis earned revenue of $2.5 million related to a milestone payment from Novartis, and $293,000 in revenue related to the shipment of Vitravene. Isis earned no revenue related to Vitravene during 2004 and 2003.

Ibis Collaborations

To develop the TIGER technology and applications, our Ibis division has received contracts from a number of government agencies, including DARPA, the NIAID, part of the NIH, the CDC and the FBI. Each of these agencies represents a significant source of funding for its TIGER program. To date, the Ibis division has earned $40.1 million in revenue under its government contracts and grants. Also, it has approval to invoice its government partners an additional $8.6 million under its existing contracts and grants. The Ibis division may receive continued approval to invoice its 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 awards. The Ibis division has received contracts and grants from numerous government agencies valued at up to $63.2 million.

In October 2004, Isis was granted three government contracts valued at up to $10.0 million from the NIAID, the FBI and an undisclosed government agency for the continued development of our TIGER system. Under the NIAID award, Isis intends to develop an application to use its TIGER technology to assess the safety of investigational vaccines and the components used for the manufacturing of biological products by identifying foreign infectious organisms that may be present. Under the FBI award, Isis will continue ongoing development of a microbial agent database.

Isis receives funding from DARPA through a subcontract with SAIC, on a multi-year project for the ongoing development of TIGER. This project combines Isis' expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal processing capabilities. In March 2004, Isis entered into a two-year contract with SAIC that provides for up to $19.5 million in funding by DARPA. During 2004 and 2003, revenue from SAIC comprised 18% and 16%, respectively, of Isis' total revenue.

In September 2003, Isis received a three-year grant for up to $6.0 million from the CDC to develop and apply the TIGER technology to the surveillance of human infectious disease in the United States. Using the grant from the CDC, Isis expects to develop and provide TIGER technology for CDC projects focused on emerging human infectious disease.

Licensing Agreements

Eyetech Pharmaceuticals, Inc.

In December 2001, Isis licensed to Eyetech, a publicly-held company, certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense compound intended for use in the treatment of ophthalmic diseases. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis. In December 2002, Eyetech entered into an agreement with Pfizer to develop and commercialize Macugen.

During 2004, Isis earned from Eyetech $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 also may generate additional milestone payments aggregating up to $2.8 million based on achieving specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication.

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 aggregate payments of $24.0 million over the next three years. Under the terms of the agreement, Isis and DRC will 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 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% of all royalties on annual sales in excess of $1.0 billion and 100% 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 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. 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 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.

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, 2004 and 2003 reflected a licensing asset, net of amortization, of $21.3 million and $23.2 million, respectively, and a short-term investment at fair market value of $474,000 and $1.1 million, respectively, related to this agreement. Early in 2005, Isis liquidated its short term investment for cash proceeds of $655,000.

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 $4.2 million through December 31, 2004 and expects to pay IDT an aggregate of $700,000 in 2005.

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"*).

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.

During 2002, Isis earned revenue of $3.0 million from HepaSense, and $8.9 million from Orasense, which Isis included in its consolidated statements of operations as research and development revenue from affiliates. During 2002, Isis recorded $6.5 million as equity in the loss of HepaSense, and $9.5 million as equity in the loss of Orasense. As of December 31, 2004 and 2003, Isis had no receivable or funding obligation related to Orasense or HepaSense.

7. Segment Information and Concentration of Business Risk

Segment Information

Prior to 2004, the Company managed itself on a fully integrated basis in one operating segment. As a result of the technological and organizational advances that Isis' Ibis division made during 2004, combined with the future commercialization plans for its TIGER program and the significant contribution that it made to Isis' 2004 revenue, Isis believes it is appropriate to discuss the financial results of its Ibis division as a separate operating segment. In addition, based upon the distinct nature of the products and services each segment provides, Isis determined that it operates in two reportable segments, Drug Discovery and Development, and Ibis. Segment operating loss includes research and development, general 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 drug candidates for optimal use with particular targets and thus, to produce a broad proprietary portfolio of compounds applicable to many disease targets.

The Ibis segment 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. Within the Ibis division, the Company has invented a technology that has the potential to revolutionize the identification of infectious diseases. This technology is called TIGER, which is the product of core technology development and small molecule drug discovery research conducted within the Ibis division during its early years. Prior to the development of TIGER, the Ibis division focused on discovering novel small molecule antimicrobial drugs.

Prior to 2004, Isis did not allocate R&D support or general and administrative costs to its operating segments. Isis believes 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, Isis has not presented segment financial information for periods prior to 2004. 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 year ended December 31, 2004.

Revenue:	Drug Discovery and Development	Ibis	Corporate	Total
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)

Geographic Information

Revenue by geographic area for the year ended December 31, 2004 is as follows:

US	$ 41,124
Singapore	1,500
Total	$ 42,624

Long-lived assets by geographic area as of December 31, 2004 are as follows:

US	$ 82,515
Singapore	301
Total	$ 82,816

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:

	2004	2003	2002
Partner A	37%	62%	57%
Partner B	18%	16%	0%
Partner C	13%	0%	0%
Partner D	0%	0%	11%

During 2004, 2003 and 2002, Isis derived approximately 28%, 20% and 7%, respectively, of its revenue from agencies of the United States Government, including approximately 18%, 16% and zero, respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 30%, 20%, 17% and 10% of contract receivables at December 31, 2004. Contract receivables from three significant partners comprised approximately 49%, 17% and 15% of contract receivables at December 31, 2003.

8. Restructuring Activities

During the fourth quarter of 2004, Isis recorded a $32.4 million non-cash charge for restructuring activities resulting from management's strategic decision to reorganize and refocus the Company's resources to advance its most promising second-generation drugs and to continue its development of antisense technology. As a result, in 2004 Isis recorded write-downs which approximated the carrying value of tangible and intangible assets considered non-essential to the Company's current focus. These charges are summarized below:

	Year Ended December 31, 2004 (in thousands)
Excess or idle equipment costs	$ 1,161
Write-down of inventories to estimated net realizable value	20,972
Write-down of prepaid expenses to estimated net realizable value	4,149
Write-down of patent costs to estimated net realizable value	6,145
Total	$ 32,427

In connection with the decision to reorganize and refocus the Company's resources, 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. Isis expects to complete these restructuring efforts by the end of the second quarter 2005. Pursuant to SFAS No. 146, *"Accounting for Costs Associated with Exit or Disposal Activities,"* Isis expects to record the majority of these charges during the first quarter of 2005.

In April 2003, Isis initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, Isis had a small reduction in its workforce, which primarily represented positions that Isis used to support the commercialization and manufacture of Affinitak. Consequently, Isis incurred a restructuring charge of approximately $1.8 million during the second quarter of 2003. Isis completed the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

In November 2002, Isis announced the termination of the GeneTrove database product offering and the resulting reorganization of the GeneTrove program. As a result, Isis had a small reduction in workforce. The restructuring plan also provided for the write-down of certain intellectual property. As a result of this plan, Isis recognized restructuring related charges of approximately $1.4 million as operating expenses in the fourth quarter of 2002. Isis fully utilized the reserve related to this restructuring in the fourth quarter of 2003.

9. Employee Postemployment 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 ($13,000 and $16,000 in 2004 for employees under 50 years old and over 50 years old, respectively). Isis made approximately $478,000 and $463,000 in matching contributions for the years ended December 31, 2004 and 2003, respectively.

10. Affiliate Supplementary Disclosure

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in Orasense under the equity method of accounting through 2002. At inception, Elan granted Orasense a license to its intellectual property for $15.0 million. The term of the license was three years and amortization expense related to this license was $1.3 million for the year ended December 31, 2002. Through December 2002, Orasense incurred research and development expenses, performed by Elan and Isis on Orasense's behalf, in the course of its product development. In conjunction with its restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002. As a result, 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. Through the agreement, Isis eliminated all future royalties to Elan related to the technology for the formulation of oral drugs developed within the Orasense collaboration.

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.

The following table presents summary financial information for Orasense as of and for the year ended December 31, 2003 (in thousands, except per share amounts)

Balance Sheet:	
Assets	
Cash and cash equivalents	$ 6
Total assets	$ 6
Liabilities and Stockholders' Equity	
Amounts due to affiliates	$ —
Common stock, $1.00 par value; 12,000 authorized, issued and outstanding at December 31, 2003	12
Additional paid-in capital	50,129
Accumulated deficit	(50,135)
Total liabilities and stockholders' equity	$ 6
Results of Operations:	
Revenue	$ —
Research and development expenses	4,207
Total operating expenses	4,207
Net loss	$ (4,207)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in HepaSense under the equity method of accounting through 2002. At inception, Elan granted HepaSense a license to its intellectual property for $15.0 million. The term of the license was three years and amortization expense related to this license totaled $5.0 million for the year ended December 31, 2002. HepaSense incurred research and development expenses, performed by Elan and Isis on Hepasense's behalf, in the course of its product development. In conjunction with its restructuring efforts, Elan concluded its participation in the HepaSense collaboration in 2002 and Isis regained all rights to ISIS 14803. As a result of the collaboration termination, there was no activity during the years ended December 31, 2004 and 2003.

In June 2004, Isis acquired Elan's minority interest in HepaSense. Through the agreement, Isis eliminated all future royalties to Elan related to ISIS 14803.

The following table presents summary financial information for HepaSense as of and for the year ended December 31, 2003 (in thousands, except per share amounts):

Balance Sheet:	
Assets	
Cash and cash equivalents	$ 4
Total assets	$ 4
Liabilities and Stockholders' Equity	
Common stock, $1.00 par value; 6,001 shares authorized, issued and outstanding at December 31, 2003	$ 6
Series A Preferred stock, $1.00 par value; 6,000 shares authorized, issued and outstanding at December 31, 2003	6
Additional paid-in capital	26,221
Accumulated deficit	(26,229)
Total liabilities and stockholders' equity	$ 4

11. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2004, and 2003 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2004 Quarters				
Revenue	$ 12,303	$ 9,843	$ 9,093	$ 11,385
Operating expenses (1)	34,638	31,183	31,473	63,183
Loss from operations (1)	(22,335)	(21,340)	(22,380)	(51,798)
Net loss (1)	(26,306)	(25,949)	(32,708)	(57,540)
Accretion of dividends on preferred stock	(181)	(180)	—	—
Net loss applicable to common stock (1)	$ (26,487)	$ (26,129)	$ (32,708)	$ (57,540)
Basic and diluted net loss per share(3)	$ (0.47)	$ (0.47)	$ (0.57)	$ (1.00)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2003 Quarters				
Revenue	$ 13,980	$ 15,017	$ 11,294	$ 9,699
Operating expenses (2)	32,892	34,536	30,361	31,179
Loss from operations (2)	(18,912)	(19,519)	(19,067)	(21,480)
Net loss (2)	(24,321)	(23,097)	(22,203)	(25,375)
Accretion of dividends on preferred stock	(171)	(172)	(175)	(176)
Net loss applicable to common stock (2)	$ (24,492)	$ (23,269)	$ (22,378)	$ (25,551)
Basic and diluted net loss per share(3)	$ (0.44)	$ (0.42)	$ (0.40)	$ (0.46)

(1) Loss includes charges related to restructuring activities of $32.4 million incurred during quarter ended December 31, 2004.

(2) Includes charges related to restructuring activities of $1.8 million incurred during the quarter ended June 30, 2003.

(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.

12. Subsequent Events

Legal Matters

On or about January 27, 2005, Ajinomoto Co., Inc. ("Ajinomoto") filed a Demand for Arbitration against Isis with the American Arbitration Association in San Diego, California. The Demand relates to a 1994 license agreement between Ajinomoto and Isis, which purports to license certain intellectual property 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 Isis are covered by the license and seeks a determination of products covered by the license, along with an accounting of any sums due as a result. Ajinomoto alleges these sums amount to no less than $3.9 million. Ajinomoto also seeks a determination that the license is still in force. Isis strongly believes that it has not developed any products covered by the license, and intends to vigorously defend the claim. A hearing on this matter has not yet been set. Isis estimates that the potential range of loss on this claim is zero to $2.1 million, and believes it is reasonably possible, but 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, 2004.

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 and Form S-8 Nos. 333-116962, 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-43330, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859) of Isis Pharmaceuticals, Inc. and in the related Prospectuses of our reports dated March 3, 2005, with respect to: (1) the consolidated financial statements of Isis Pharmaceuticals, Inc., and (2) 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, 2004.

/s/ Ernst & Young LLP

San Diego, California
March 10, 2005

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 15, 2005

/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: Match 15, 2005

/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, 2004, 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 15, 2005

/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.

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Stanley T. Crooke, M.D., Ph.D.
CHAIRMAN AND CEO

DEAR STOCKHOLDERS,

Isis and our growing list of partners have led in the advancement of all areas of antisense drug development, from basic research to drug discovery to clinical development to commercial-scale manufacturing.

THESE ADVANCES ARE EVIDENCED BY THE:

- Number of antisense drugs in development;
- Number of companies participating in development of these drugs;
- Range of diseases in which we are studying antisense drugs;
- Significant reductions in the cost to deliver antisense drugs;
- Invention of improved second-generation chemistries, and
- Development of many routes of administration for antisense drugs, including the potential for oral and aerosol delivery.

Through our investment, innovation and passion, we have created antisense technology; a technology that allows us to efficiently generate drugs for ourselves and our partners. Our second-generation drugs represent the future of Isis and the technology. We are committed to broadening the applications for antisense, while taking advantage of the technology's productivity and capitalizing on the drug assets that arise from our drug discovery and development programs.

Our business strategy is designed to take advantage of our knowledge and expertise in RNA-based drug development and the strengths of our technology, patent position, employees and management team to advance multiple drug candidates toward the market. We plan to execute this strategy by licensing our drugs as early in the clinical development process as we can on the best terms possible. This strategy allows us to participate in the progress of many drugs as they move through the clinic, while decreasing our investment in any one product. Further, by increasing the number of antisense drugs in development, we significantly increase the probability of multiple commercial successes.

As we enter 2005, we have all the elements in place to continue to implement this strategy. We have an exciting pipeline, excellent partners, and more than 1,500 issued or exclusively licensed patents, all of which provide us with a sound leadership position in oligonucleotide-based therapeutics. We have built the infrastructure necessary to efficiently and effectively discover and develop antisense drugs. And, along the way, we have advanced our TIGER biosensor system to an important stage in its development. We are optimistic about the prospects of the Company and the therapeutic and commercial potential of each one of our products in development. What remains is for us to execute our 2005-2006 plan by achieving the following objectives:

FIRST, WE MUST FIND A STRONG PARTNER FOR ALICAFORSEN ENEMA, AND AGGRESSIVELY MOVE THIS NEAR-TERM PRODUCT OPPORTUNITY TOWARDS THE MARKET.

In late 2004, we announced data from three Phase 2 clinical trials of alicaforsen enema involving more than 300 patients with ulcerative colitis (UC). These trials demonstrate the drug improves signs and symptoms of UC and is well-tolerated. In the Phase 2 studies, alicaforsen enema outperformed both placebo and the enema standard-of-care. As a result, we now have the information we need to plan a Phase 3 development program. We believe alicaforsen enema represents an attractive commercial opportunity for Isis. If the activity, durability and safety results demonstrated in the Phase 2 trials are replicated in late-stage trials, we believe alicaforsen enema will be an important new drug for patients with this disease.

Our goal in 2005 is to meet with the U.S. Food and Drug Administration to discuss Phase 3 clinical trial plans for alicaforsen enema, identify the best marketing partner with

late-stage development and commercial expertise, and work with that partner to develop and implement a successful Phase 3 program. This strategy should allow us to benefit from a partner's clinical trial experience and knowledge, and avoid the significant costs associated with late-stage development. In turn, we will focus our resources and unique strengths on advancing our second-generation drugs.

SECOND, WE PLAN TO ADVANCE OUR TWO KEY SECOND-GENERATION DRUGS, ISIS 301012 AND ISIS 113715, TO CLINICAL PROOF-OF-VALUE.

ISIS 301012, a drug that inhibits apoB-100 for the treatment of high cholesterol, is an important asset. ISIS 301012 administered subcutaneously is completing Phase 1 studies. Last year, we reported data from this Phase 1 trial that showed ISIS 301012 produces dose-dependent, rapid and prolonged reductions of its target, and in LDL, VLDL and total cholesterol levels in volunteers with borderline elevated cholesterol. Further, these data demonstrate that ISIS 301012 is working as designed; it inhibits and reduces its intended target, resulting in the predicted therapeutic pharmacological outcome, the lowering of cholesterol. Importantly, we have also demonstrated that an oral form of the drug reduces cholesterol in animals. These results gave us the confidence to initiate a Phase 1 trial of the oral formulation of ISIS 301012 in March 2005.

In 2005–2006, through our development of both the subcutaneous injection and oral formulations of ISIS 301012, we plan to:

- define the optimal dose and schedule for ISIS 301012 as a single agent;
- prepare for the initiation of combination studies with oral lipid-lowering drugs;
- define the oral bioavailability of ISIS 301012 and demonstrate reduction of apoB-100 and cholesterol in man;
- advance ISIS 301012 into additional clinical trials to evaluate longer-term dosing, and
- explore other indications, such as therapeutic apheresis, that may offer shortened routes to commercialization.

Consistent with these goals, we plan to:

- report final results from the ongoing Phase 1 single agent study in normal volunteers with borderline elevated cholesterol;
- initiate a Phase 2 trial to evaluate dose and dose schedule in patients with high cholesterol;
- initiate a pharmacokinetic study to evaluate the addition of ISIS 301012 to statin therapy, and
- initiate a Phase 2 study in patients with high cholesterol who are also taking statins.

ISIS 113715, a drug that inhibits PTP-1B for the treatment of type 2 diabetes represents another significant product opportunity. This drug is in Phase 2 clinical trials. In a Phase 1 study, ISIS 113715 increased insulin sensitivity in normal volunteers. Subjects treated with ISIS 113715 did not experience hypoglycemia, or excessively low blood sugar, which is an adverse effect observed with many currently available type 2 diabetes treatments.

The goals of our ISIS 113715 development program in 2005-2006 are to:

- demonstrate the safety of the drug as a single agent in patients with type 2 diabetes to support longer-term dosing;
- define the optimal dose and schedule to support future clinical trials;
- advance ISIS 113715 into additional clinical trials to evaluate longer-term dosing, and
- explore the drug in patients who are also taking oral anti-diabetic therapies.

In line with these goals, we plan to:

- report results from the ongoing Phase 2 single agent trial in patients with type 2 diabetes;
- report results following 12 weeks of dosing in patients with this disease, and
- initiate dosing in patients with type 2 diabetes who are also taking oral anti-diabetic therapy.

THIRD, WE INTEND TO CAPTURE VALUE FROM OUR PORTFOLIO OF SECOND-GENERATION ANTISENSE PRODUCT OPPORTUNITIES AND CONTINUE OUR ADVANCEMENT OF THE TECHNOLOGY.

In our internal development initiatives, we plan to focus our drug discovery efforts on molecular targets that give us early clinical proof-of-value and have the potential to be exciting new drugs that address numerous therapeutic areas with major market potential. Specific areas we are concentrating on include inflammatory, metabolic and cardiovascular diseases, and cancer. In 2005-2006, we intend to advance at least two new drug candidates from our drug discovery programs into development.

FOURTH, WE PLAN TO EXPAND OUR PARTNERS' DEVELOPMENT PIPELINES AND SUPPORT THE CONTINUED ADVANCEMENT OF CURRENTLY PARTNERED SECOND-GENERATION DRUGS.

We are pleased with the progress made within our current collaborations and our achievements in establishing new ones. Our overall goal in working with partners is to participate in advancing their products through the clinical development process and toward the market.

In 2004, we extended our anti-cancer drug discovery collaboration with Eli Lilly and Company and reported continued progress within our alliance throughout the year. Lilly initiated a Phase 1 trial of LY2181308 in patients with cancer. LY2181308 is the first drug from our alliance to enter the clinic. This second-generation antisense drug targets survivin, a molecule that allows cells that would normally undergo programmed cell death to survive. We also licensed LY2275796 to Lilly in September 2004, the second antisense anti-cancer drug to emerge from the Isis-Lilly collaboration. LY2275796 targets eukaryotic initiation factor-4E, a protein involved in the growth and progression of tumors. This drug is in preclinical development. For these accomplishments we earned $2.25 million in milestone payments from Lilly.

In 2005-2006, our goal is to support the continuation of Lilly's anti-cancer antisense research and development programs. Further, we are optimistic we will add new antisense drug candidates to Lilly's oncology franchise, and plan to continue to discover and advance additional compounds for licensing consideration by Lilly.

We have also successfully engaged in other strategic drug discovery and development collaborations, which we call our satellite company partnerships. Satellite companies allow us to benefit from our partners' expertise and highly focused research efforts. In turn, partners gain from our experience and expertise in RNA-based drug discovery and development and access to our proprietary antisense chemistries and leading intellectual property. We currently work with high-quality life sciences companies such as OncoGenex Technologies, Inc., Antisense Therapeutics Limited (ATL), Alnylam Pharmaceuticals, Inc., Santaris Pharma A/S and Sarissa, Inc.

OncoGenex has been a partner since 2001. This collaboration combines OncoGenex's proprietary antisense position in inhibitors to the cancer target clusterin, with our proprietary second-generation antisense chemistry. The lead drug in this collaboration is OGX-011 which targets clusterin, a cell survival protein that when overproduced, prevents cancer cell death and counters the effectiveness of standard anti-tumor treatments. Currently, we are supporting OncoGenex's OGX-011 development initiatives. In June 2004, the partnership reported that OGX-011 was well-tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91% dose-dependent reduction of its target in a Phase 1 trial.

In 2003, we expanded our partnership with OncoGenex to include the development of OGX-225, the first bi-specific antisense inhibitor to enter development. A bi-specific inhibitor is a single-stranded antisense drug designed to inhibit the production of two proteins simultaneously. OGX-225 targets both insulin-like growth factor binding protein-5 and insulin-like growth factor binding protein-2, two molecules involved in the development of metastatic disease in hormone-regulated tumors. OGX-225 is in the research phase of development. Recently, we again expanded our collaboration with OncoGenex to allow for the development of two additional second-generation antisense drug candidates for cancer.

In 2005-2006, we will support OncoGenex's expansion of OGX-011 development into additional cancer therapeutic areas through the completion of a second Phase 1 trial evaluating OGX-011 in combination with TAXOTERE® in solid tumors, and the initiation of Phase 2 clinical trials of the drug in patients with lung, breast and prostate cancers.

ATL is an Australian-based antisense company we helped found in 2001. We are supporting ATL's development efforts to determine the potential of ATL 1102 as an effective treatment for multiple sclerosis (MS). ATL 1102 is an antisense inhibitor of VLA-4. ATL 1102 entered a Phase 2a clinical trial in patients with MS after positive findings from an earlier trial. In March 2005, ATL announced that, although it and the trial investigators are confident that the current ATL 1102 Phase 2a trial is safe, in light of recently announced safety issues associated with another VLA-4 inhibitor that works through a different mechanism, ATL decided to halt the current trial. ATL plans to convene an advisory group to consider the potential development path for ATL 1102.

In 2004, ATL also initiated a proof-of-concept study to explore the activity of ATL 1101 in patients with psoriasis. ATL 1101 is a second-generation antisense drug designed to block the synthesis of the insulin-like growth factor-1 receptor, a protein involved in the regulation of cell growth in psoriasis.

In 2005-2006, we will support ATL's ongoing development efforts to determine the potential of ATL 1102 for MS and to explore the activity of ATL 1101 in psoriasis.

Alnylam is a partnership focused on a particular antisense mechanism of action called RNAi or siRNA. Alnylam is widely considered to be the center of excellence for RNAi research and therapeutic development. In 2004, we formed a strategic alliance with Alnylam to accelerate the development and commercialization of RNAi therapeutics. This alliance combines our expertise in antisense drug development, antisense mechanisms of action and oligonucleotide chemistry with Alnylam's expertise in RNAi therapeutics.

In this transaction, we licensed to Alnylam our patent estate relating to antisense mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs and downstream milestone and royalty payments. We have already realized value from this alliance through the receipt of a $500,000 license fee from Alnylam related to Alnylam's partnership with Merck to develop and commercialize RNAi therapeutics for ocular diseases. Recently, we and Alnylam expanded our strong patent positions in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of microRNA.

Sarissa, a Canadian biotechnology company emerging from the University of Western Ontario, is our most recent satellite company relationship. In February 2005, we licensed an anti-cancer antisense drug to Sarissa. The licensed drug is an antisense inhibitor of thymidylate synthase, a well-known drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of thymidylate synthase suppressed human tumor cell growth and overcame tumor cell resistance to marketed thymidylate synthase-targeted drugs. This drug is in the research phase of development.

We will support Sarissa's development efforts by providing them with access to our RNA-based drug discovery and development expertise. This partnership, similar to the one we have with OncoGenex, combines our second-generation chemistry and experience in antisense discovery and development with Sarissa's deep understanding of the biological role of thymidylate synthase and oncology expertise.

FIFTH, OUR GOAL IS TO CONTINUE THE DEVELOPMENT OF OUR TIGER BIOSENSOR SYSTEM, AND IMPLEMENT A BUSINESS PLAN TO TAKE ADVANTAGE OF THE MANY COMMERCIAL PRODUCT OPPORTUNITIES AVAILABLE FOR TIGER.

We have continued to make excellent progress in advancing core TIGER (Triangulation Identification Genetic Evaluation of Risks) technology, and in creating new applications for the TIGER biosensor system.

During 2004, the TIGER team made remarkable technology and system engineering advances that strengthened the potential commercial opportunities for this system. Our scientists added application development for epidemiological surveillance and biological products screening, and continued to expand our microbial agent database to support broader uses of the TIGER biosensor system. The bioweapons defense, epidemiological surveillance and biological products screening applications of our TIGER technology represent the first of many we plan to develop for the TIGER system to enhance its commercial value and opportunity in the government, research, and medical and diagnostic markets.

Our goals for the TIGER program in 2005–2006 are to continue to:

• secure government contracts;

• deploy TIGER biosensor systems to our government partners, and

• execute a business plan to successfully market TIGER's products and services to both government and non-government commercial customers.

SIXTH, WE PLAN TO CONTINUE TO CAPITALIZE ON OUR INTELLECTUAL PROPERTY ESTATE.

The most important aspect of our patent estate is that it protects our drugs in development, while supporting substantial long-term control of oligonucleotide-based therapeutics. We have been very successful in licensing our patent estate and have used it wisely to enter into a number of strategic relationships. To date, we have generated nearly $70 million from licensings, which helps fund our drug discovery and clinical development programs. Our highly productive oligonucleotide chemistry program and patents arising from it should continue to provide significant licensing opportunities in the future.

In conclusion, we have created the right chemistry for success. The ideal mix of:

• exciting drugs in various stages of development with significant commercial potential;

• a sustainable portfolio of new product opportunities waiting to be developed;

• a strong blend of partnerships that encompass all areas of our business and are dedicated to increasing the use of our technologies in the marketplace;

• deep antisense drug discovery and development expertise;

• a strong management team, and

• a leadership position in RNA-based technology development that is unmatched.

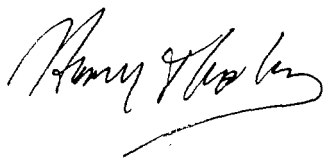
The ongoing advancement of a technology that could significantly improve the efficiency of drug discovery and development and yield fundamentally different, improved drugs for patients is a substantial challenge. We have made great progress, but we have more to do. As we achieve our goals in the coming year, we will be significantly closer to bringing RNA-based products to market. We thank you for your continued interest in Isis and your support of our endeavors.

In an additional effort to contain costs, we are providing this letter along with our Annual Report on Form 10-K as a simplified version of our 2004 Annual Report. An on-line version of the Isis 2004 Annual Report is available on our web site at **www.isispharm.com**. The online version of our Annual Report is an interactive, multimedia discussion of the Company and its businesses. I hope you enjoy reading it.

You may also contact our Investor Relations and Corporate Communications Department at 760-603-2331, or by email at **info@isisph.com**, to request the Isis 2004 Annual Report, either on a CD-Rom or in hard copy, be sent to you free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Sincerely,



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a division of Isis

Corporate Headquarters

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

TELE 760.931.9200
ONLINE www.isispharm.com
EMAIL info@isisph.com

TRANSFER AGENT

American Stock
Transfer & Trust
59 Maiden Lane
New York, NY 10038

OUTSIDE LEGAL COUNSEL

Cooley Godward LLP
4401 Eastgate Mall
San Diego, CA 92121

CHIEF PATENT COUNSEL

Woodcock Washburn LLP
One Liberty Place
46th Floor
Philadelphia, PA 19103

INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Ernst & Young LLP
501 W. Broadway,
Suite 1100
San Diego, CA 92101

COMMON STOCK SYMBOL

NASDAQ: ISIS

FORWARD-LOOKING STATEMENT

This annual report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, 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 Isis' clinical 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 technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. 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. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include but are not limited to, those discussed in Isis' Annual Report on Form 10-K for the year ended December 31, 2004, which is on file with the U.S. Securities and Exchange Commission, and available from the company.