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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 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, 2001

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.)

2292 Faraday Ave., 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 o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. Yes ☒ No o

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 $646,593,996 as of February 28, 2002. *

The number of shares of voting common stock outstanding as of February 28, 2002 was 53,958,465.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Registrant's definitive Proxy Statement filed on or about April 5, 2002 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 31, 2002 is incorporated by reference into Part III of this Report.

*Excludes 9,882,528 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 February 28, 2002. 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.

This Form 10-K contains forward-looking statements regarding our business 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. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Form 10-K. Factors that could cause or contribute to such differences include, but are not

limited to, those discussed in this Form 10-K including those identified in the section of Item 1 entitled "Risk Factors". As a result, you should not rely on these forward-looking statements.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company pioneering 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 that it needs to produce proteins, including those proteins that are involved in disease. Interference with RNA can keep the body from producing proteins that are involved in disease. We have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors designed to bind with high specificity to their RNA target and modulate protein production. With our Ibis technology, we use our expertise in RNA to design small molecule therapeutics that bind to RNA. We also use our antisense technology in collaborations with pharmaceutical companies to identify and prioritize attractive gene targets for their drug discovery programs. We believe we have established a leadership position in exploiting RNA as a target for drugs.

We used our antisense technology to commercialize our first product, Vitravene®. Vitravene demonstrates our ability to meet FDA regulatory requirements and to manufacture commercial antisense drugs. We have 13 products in our development pipeline with eight in human clinical trials designed to assess safety and efficacy. Our products in development address numerous therapeutic areas with major market potential, including cancer and inflammatory, viral, metabolic and dermatological diseases. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. Our second-generation drugs, which represent approximately half of our drugs in development, may be able to be dosed as infrequently as once per month. We are also making progress on oral formulations for our second-generation drugs.

LY900003 (ISIS 3521), our most advanced product in development, is undergoing Phase III clinical trials in combination with traditional cancer chemotherapy drugs to treat non-small cell lung cancer, the most common form of lung cancer. In January 2002, we completed enrollment of a 600 patient Phase III trial that we initiated in late 2000. We initiated this trial based on promising results in a Phase II trial in patients with non-small cell lung cancer. Results from the Phase II study showed a median survival time of 15.9 months in patients using our drug in combination with standard chemotherapy. The typical median survival time of similar cancer patients receiving standard chemotherapy alone is approximately seven or eight months. If the data from our Phase III trial are sufficiently positive to support a single study New Drug Application, or NDA, we and Lilly plan to file the NDA in 2003. If two Phase III studies are required, we and Lilly plan to file the NDA in 2004. In November 2000, the FDA granted LY900003 (ISIS 3521) fast track review status. In November 2001, we initiated a Phase III clinical trial for another product, ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. We have six additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide pharmaceutical companies with important information about genes that these companies are interested in targeting for their drug discovery programs. We provide this information rapidly and efficiently, using the same proprietary methods and systems that we developed to create antisense drugs. We are collaborating with nine major pharmaceutical partners for these services, including Abbott Laboratories, Inc.; Amgen Inc.; Aventis (Rhone-Poulenc Rorer); Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; Johnson & Johnson Pharmaceutical Research & Development, LLC; Merck & Co., Inc. and Pharmacia Corporation. We supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product. This database will contain proprietary information about the function of thousands of genes, which we believe pharmaceutical companies will find valuable

in designing and prioritizing their drug discovery programs. Our GeneTrove division is generating near-term revenues while enhancing our own antisense drug discovery efforts and our patent portfolio.

Our Ibis Therapeutics division designs small molecule drugs that work by binding to RNA, in contrast to traditional drugs, which bind to proteins. Our scientists have invented methods of identifying RNA targets and screening for drugs that bind to RNA. Beyond its therapeutic focus, Ibis has expanded the application of its technology to develop a new diagnostic platform to detect infectious agents. Since its inception, Ibis has received significant financial support from various federal government agencies to use its technology for the development of RNA-based countermeasures to biological warfare. In October 2001, Ibis received a two-year contract with the Defense Advanced Research Projects Agency, or DARPA, to develop a device to detect infectious agents used in biological warfare attacks. Under this two-year contract, for the research program Triangulation Identification Genetic Evaluation of biological Risks, or TIGER, we expect to receive up to $8.9 million in funding. In June 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a Pfizer company. In May and October 2001, we received a $2.5 million milestone payment and a $1.5 million milestone payment, respectively, under this collaboration.

We have a broad patent portfolio relating to our technologies. We have rights to nearly 900 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. In 2001, we continued to fortify our antisense technology portfolio by exclusively licensing Hybridon's antisense chemistry and delivery technology patents. 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 inventions in RNA-based drug discovery. Our intellectual property estate also enables us to expand our pipeline by granting partners limited access to antisense technology. Licensing partnerships may include antisense and Ibis drug discovery alliances such as those we have with Lilly and Amgen, GeneTrove functional genomics collaborations such as those we have with Chiron, Amgen, and Pharmacia or licenses to non-antisense patents for drug discovery such as our license to Eyetech Pharmaceuticals, Inc.

Drug Discovery and Development

Our work in RNA-based drug discovery and development has produced two important drug-discovery technologies: our primary technology, antisense, and our small molecule RNA, or Ibis, technology. From our progress in antisense we have developed a robust pipeline of promising new drugs and efficient genomics tools that unlock value from gene sequence data. Our earlier stage Ibis program has potential to become an important new approach to traditional drug discovery.

Antisense Technology Platform

Antisense Drug Discovery

Proteins are essential, working molecules in a cell. Almost all human diseases result from inappropriate protein production or improper protein activity. By preventing the production of the disease-causing protein and acting in the early stage of the disease-causing process, antisense drugs have the potential to provide greater therapeutic benefit than traditional drugs, which act after the body has produced the disease-causing protein. Traditional drugs are designed 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 targets disease-causing proteins before the body produces them. While conventional drugs bind to these disease-causing proteins, antisense drugs, or antisense inhibitors, are designed to interrupt the process of making proteins. Protein synthesis occurs in two phases: transcription and translation.

The information necessary to produce proteins in cells is contained in genes, the instruction manuals of the body. A specific gene contains information to produce a particular protein. A gene is made up of bases or nucleotides that are arranged in a two-stranded structure that resembles a twisted ladder, known as deoxyribonucleic acid, or DNA. The specific sequence of bases spells out the instructions for producing a particular protein. The bases on one side of the ladder bind weakly to complementary bases on the other strand creating the ladder's rungs. This highly specific nucleotide pairing is the key for information transfer from DNA to its intermediary, messenger RNA, or mRNA. This information transfer is called transcription.

During transcription of information from DNA into mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template, and information stored in the DNA strand is copied into mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, its mRNA's base 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.

Using the information contained in mRNA, we design chemical structures, called oligonucleotides, which resemble DNA and are the complement of mRNA. These potent antisense oligonucleotides inhibit the production of disease-causing proteins. Antisense drugs can selectively inhibit one protein among a closely related group of proteins without having an impact on the other members of the group, because antisense drugs interact based on very specific binding sequences found in RNA. It is easier to differentiate between closely related proteins at the RNA sequence step 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 selectivity means that antisense drugs may be far 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 usually begins by characterizing the three-dimensional structure of the protein target in order to design a prototype drug to interact with it. Proteins are complex molecules with structures that are difficult to predict. Antisense compounds, on the other hand, are designed to bind to mRNA structures, which are more easily understood and predicted. We can design prototype antisense drugs as soon as we identify the sequence for the mRNA receptor.

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 advancements in chemistries, which we call our second-generation antisense drugs, that have increased the potency, stability, oral bioavailability and side effect profile of this new class of drugs. We have also made significant progress in developing new formulations, such as oral, topical cream, intravenous, subcutaneous, intravitreal, aerosol and enema, of antisense drugs that, again, expand the potential for antisense.

GeneTrove Target Validation and Gene Functionalization

GeneTrove is our functional genomics division, which commercializes the first step of our antisense drug discovery program. GeneTrove capitalizes on the specificity of antisense, using it as a tool to identify what a gene does, which is called gene functionalization, and to determine whether a specific gene is a good target for drug discovery, which is called target validation. GeneTrove provides valuable functional genomics services to the pharmaceutical and biotechnology industries, enhancing and expediting drug discovery and development decisions, and generating near-term revenue for us in the process.

Current technologies used to determine a gene's value as a drug target are limited in their ability to verify the role of a particular gene in human disease and uncover the feasibility of a specific target in a biological system. Antisense technology, however, is an important technology platform for conducting biological studies and is an effective, rapid, and relatively inexpensive method of gene functionalization.

GeneTrove can create highly specific antisense inhibitors to a particular gene for use in cell culture studies in a matter of days. Scientists can use GeneTrove inhibitors in a broad variety of cell types and animal models. GeneTrove has created inhibitors to hundreds of genes, validated multiple targets and dissected numerous disease pathways. Our strong antisense patent estate, and the Human RNase H patent in particular, have strengthened GeneTrove's competitive position. Human RNase H is a cellular enzyme that degrades RNA when antisense inhibitors bind to RNA. Most antisense inhibitors work through this mechanism of action. Our patent covers its use as a genomics tool.

Additionally, GeneTrove, using antisense technology, facilitates rapid, meaningful gene-related patenting. Conducting biological studies to determine cause/effect relationships between changes in gene expression or function, and phenotypic or disease outcome is a direct route to establish gene-related intellectual property.

Our business strategy for GeneTrove involves three major components:

- *Custom Target Validation collaborations*—research tailored to our customers' interests in identifying the role and value of specific genes as drug targets. Program participants include Abbott Laboratories, Amgen, Aventis, Celera Genomics, Chiron, Johnson & Johnson, Lilly, Merck and Pharmacia.

- *Human Gene Function Database and Antisense Inhibitor Library*—offering will help partners prioritize genomic information to rapidly identify and discover new drug targets. We expect that the database will contain information on 10,000 human genes from antisense inhibition studies in more than 40 pharmacological assays initially focused on cancer, angiogenesis, inflammation and metabolic diseases.

- *Functional genomics intellectual property licensing program*—initiative encourages industry partners to work with GeneTrove to functionalize and validate gene targets through the use of our antisense technology. Our GeneTrove functional genomics patent suite contains more than 50 patents, a subset of our overall intellectual property estate. As part of target validation collaborations with GeneTrove, Amgen, Chiron and Pharmacia have taken licenses to specific patents within this suite.

We have based GeneTrove's antisense target validation and gene functionalization program on our expertise in producing highly specific antisense inhibitors to genes and on a variety of specialized technologies that we have created and/or integrated. Scientists can use our antisense inhibitors in cellular assays and in animal models of disease to rapidly determine the pharmacological impact of inhibiting the expression of a single gene target and to determine the role of the targeted gene in human disease. Once we have shown that a target is important in human disease, traditional drug

discovery can be used to develop drugs to inhibit the target, or the specific antisense inhibitor used to validate the target can be rapidly developed as a drug.

Specialized technologies employed by our GeneTrove division include:

- *A proprietary automated rapid throughput screening process that streamlines the creation of optimized, target-specific antisense inhibitors.* We are using this system to identify antisense inhibitors to approximately 10,000 gene targets over the next several years. We are filing patent applications on the most important of these gene targets, thus expanding our proprietary position in gene function and antisense.

- *Libraries of antisense inhibitors to identify novel gene function.* With hundreds, and planned thousands, of validated antisense inhibitors to individual genes in our library, we are able to screen the library to determine the function of individual genes in cell-based assays. Results from these screens can provide novel insights into functions of poorly understood genes, potentially identifying which genes are involved in disease. We are using this process to further expand our strong intellectual property estate.

- *In vivo validation of drug targets in animal models.* GeneTrove's scientists are testing hundreds of antisense inhibitors in animal models of disease. This data can provide definitive information on the role of these genes in models of human disease, identifying which genes are suitable targets for drug discovery. As part of the process, we not only identify which genes are therapeutically important, but also identify at a very early stage potential toxicological consequences of drugs that inhibit the gene.

- *A proprietary bioinformatics database, which will provide access to cellular phenotypic data to partners.* In August 2001, we launched our Human Gene Function Database. Over the next several years our goal is to derive data for the database from the evaluation of antisense inhibitors for up to 10,000 genes in pharmacological tests that we conduct in models of oncology, angiogenesis, inflammation and metabolism. Partners may use this data to help identify which genes are important drug targets.

Ibis Technology Platform

Ibis Therapeutics has developed technology that has the potential to revolutionize the detection and treatment of infectious disease. Ibis uses our success in RNA-targeted drug discovery and development and expands on our ability to convert genomics data into drug discovery information. The initial goal of Ibis is to discover low molecular weight, or small molecule, potentially orally bioavailable drugs, that work by binding to RNA targets implicated in disease processes. This past year, Ibis expanded its program to include a diagnostic application of its technology. In Ibis, we have developed proprietary technologies in four key areas:

1) The comparison of gene sequences across and within species to identify target sites in structured RNA;

2) The prediction of the structure of RNA from genome sequence data;

3) The rapid creation and screening of large libraries of small molecule compounds designed to bind to RNA; and

4) The screening for RNA-binding molecules using novel mass spectrometry.

In our Ibis division, we are developing and integrating genome mining software to identify RNA structural motifs in therapeutic targets of interest. We can predict the three-dimensional shape of these motifs from biochemical probes of RNA structure and molecular modeling methods. We have made a fundamental breakthrough in the development of a parallel high-throughput screening strategy to

identify small molecules that bind to RNA targets using high-resolution mass spectrometry. In a multitarget affinity/specificity screening assay, or MASS, each compound and each target RNA is labeled by its exact molecular mass. Since every small molecule is labeled uniquely, our scientists can screen a large mixture in the presence of several RNA targets simultaneously. Researchers can determine the identity of the small molecule, the RNA target that it binds, its binding affinity and the location of the binding site on the RNA in one rapid set of experiments. Using this technology, we expect to be able to screen 10,000 compounds per day against six RNA targets.

Ibis' area of focus is discovering novel antibacterial, antiviral and antifungal compounds. Our Ibis research programs also include oncology. In addition, Ibis is developing a device to detect infectious agents used in biological attacks.

In October 2001, Ibis received a contract under which we expect to receive funding of up to $8.9 million from the Defense Advanced Research Projects Agency, or DARPA, for the research program Triangulation Identification Genetic Evaluation of biological Risks, or TIGER, which is focused on the development of a diagnostic device to detect infectious agents used in biological warfare attacks. During 2001, San Diego-based Science Applications International Corporation and Ibis worked together to receive the TIGER program award. The SAIC and Ibis Therapeutics partnership combines Ibis' expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal processing capabilities.

The TIGER contract builds on the biological warfare countermeasure research Ibis has conducted in two previous DARPA programs. The preceding studies, initiated in 1997 and 1999, focused on creating a strategy to identify common binding sites, or structured regions within RNA, to a wide range of infectious agents in order to develop small molecules to combat infectious pathogens. Ibis' work for DARPA has yielded a number of proprietary targets and significant advances in RNA-targeted drug design.

In May 2001, Ibis earned a $2.5 million research milestone payment from Pfizer, for progress in Ibis' collaboration to discover small molecule drugs that bind to RNA. In October 2001, Ibis earned a second milestone payment of $1.5 million in its drug discovery program with Pfizer. Ibis earned this second milestone payment for using its proprietary technology to identify a group of small molecules that bind to previously undiscovered RNA targets.

Product Approved and Products Under Development

We have successfully developed the first antisense drug to reach the market, Vitravene, for CMV retinitis. This drug is marketed by our commercialization partner, Novartis Ophthalmics.

We have designed our drugs in development to treat a variety of health conditions, including cancer and inflammatory, viral, metabolic and dermatological diseases, and we 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 outlines our approved product and each of our products under development, its target, disease indication and development status, as well as our commercial rights.

Products in Development

Product(1)	Target	Disease indication	Development Status(2)	Commercial Rights
Vitravene(I)	Antiviral	CMV Retinitis	Approved for marketing in the U.S., Europe, Australia and Brazil.	Isis/Novartis Ophthalmics(3)
LY900003 (ISIS 3521)(P)	PKC-alpha	Cancer—Non-Small Cell Lung Cancer, Others	Phase III	Lilly
ISIS 2302(P)	ICAM-1	Crohn's Disease	Phase III	Isis
ISIS 2302(T)	ICAM-1	Psoriasis, Others	Phase II	Isis
ISIS 2302(E)	ICAM-1	Ulcerative Colitis	Phase II	Isis
ISIS 14803(P)	Antiviral	Hepatitis C	Phase II	HepaSense(4)
ISIS 2503(P)	H-*ras*	Cancer—Pancreatic, Others	Phase II	Isis
ISIS 104838(P,0)	TNF-alpha	Rheumatoid Arthritis	Phase II	Isis/Orasense(5)
ISIS 104838(T)	TNF-alpha	Psoriasis	Phase II	Isis
ISIS 113715(P)	PTP-1B	Diabetes	Preclinical	Merck
ISIS 13650(I)	C-*raf* kinase	Diabetic Retinopathy, Age-Related Macular Degeneration	Preclinical	Isis
ISIS 107248(P)	VLA-4	Multiple Sclerosis, Inflammatory Diseases	Preclinical	Antisense Therapeutics Limited
OGX-011(P)	Clusterin	Cancer—Prostate, Others	Preclinical	Isis/OncoGenex
ISIS 23722(P)	Survivin	Cancer	Preclinical	Isis

(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 have initiated toxicology and pharmacokinetic studies in animals to support the filing with the FDA of an Investigational New Drug, or IND.

(3) Novartis Ophthalmics has the exclusive right to distribute Vitravene.

(4) HepaSense is a joint venture of Isis and Elan.

(5) Orasense, a joint venture of Isis and Elan, owns the rights to oral formulations of ISIS 104838.

The following section provides more detailed descriptions of our approved product and those products under development and the disease indications they target. We also have a significant research program with the potential to yield additional development candidates in the future.

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. In the AIDS population, CMV retinitis is the primary cause of blindness. There are more than 270,000 active AIDS cases in the United States. The

introduction of new anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, has prolonged survival in HIV-infected individuals. Over the last several years, this has resulted in a decline in mortality from AIDS, accompanied by a decline in the

incidence of many opportunistic infections including CMV retinitis. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet, cidofovir and fomivirsen. Foscarnet and cidofovir are available in intravenous dosing forms only. Ganciclovir is available in intravenous and oral doses, as well as in an intraocular implant form.

Vitravene, or fomivirsen—In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Vitravene is an antisense compound, which we discovered and developed. Novartis Ophthalmics, the eye health unit of life sciences leader Novartis AG and our worldwide distribution partner for this drug, launched Vitravene in November 1998. For a more detailed discussion of this collaboration, see "Collaborative Arrangements and Licensing Agreements—Novartis Ophthalmics." In 1999, Vitravene also received marketing approval in Europe and Brazil. Vitravene has also received marketing approval in Australia**.**

Hepatitis C, or HCV

HCV represents a major public health challenge. This potentially deadly disease affects the liver and can eventually cause liver cirrhosis and death. It is estimated that almost four million people in the United States are infected with HCV and 8,000 to 10,000 people in the United States are expected to die from this disease each year. Interferon—alpha therapy, used alone or in combination with the drug ribavirin, is widely used in an attempt to eradicate this virus from chronically infected individuals. Patients with genotype 1 HCV have less than a 50% chance of having a sustained response with interferon-alpha therapy and ribavirin. Type 1 genotype is the most common genotype in the United States. Better, safer and more effective treatments are urgently needed, as current therapies have limited efficacy and potentially serious side effects.

ISIS 14803—Our antisense inhibitor of HCV, ISIS 14803, may represent a significant therapeutic advance in treating this serious viral epidemic. We designed ISIS 14803 to inhibit the replication of HCV. In March 2002, we initiated a 40 patient Phase II clinical trial of ISIS 14803 in patients with chronic HCV. This Phase II trial will evaluate the safety and tolerability of ISIS 14803 when administered by intravenous infusion. We are likely to report results from this trial by the middle of 2003. In a Phase I/II clinical trial, which we designed to evaluate both the safety and efficacy of ISIS 14803 in patients with HCV, ISIS 14803 demonstrated dose-dependent antiviral activity, decreasing viral titers, or level of virus in blood, in patients with drug resistant chronic HCV. All patients in the clinical study had the most common and drug resistant form of HCV, genotype 1, and all but one patient had failed previous interferon-based therapy. Patients in this Phase I/II clinical trial tolerated ISIS 14803 well. Patients in this study reported no serious side effects. We expect to report results from the conclusion of this trial late in 2002.

Based on the results of the above Phase II study, we plan to evaluate the potential of ISIS 14803 in a single-agent trial evaluating longer dosing periods. We are also planning a trial of ISIS 14803 in combination with pegylated interferon and ribavirin. We are considering future clinical trials of ISIS 14803 using Elan's MEDIPAD™ Drug Delivery System, a minimally invasive microinfusion pump.

We are developing ISIS 14803 under a joint venture agreement with Elan, which was signed in January 2000. The joint venture, HepaSense, was formed to develop and commercialize this novel drug for HCV while investigating delivery of the drug with Elan's proprietary MEDIPAD Drug Delivery System.

Cancer

Clinical trials of our anticancer compounds have demonstrated that antisense drugs appear to be promising cancer drugs. In these trials, 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.

LY900003 (ISIS 3521)—LY900003 (ISIS 3521), which we licensed to Lilly in August 2001, is our antisense compound in Phase III clinical development for non-small cell lung cancer. According to the American Cancer Society, lung cancer is the leading cause of cancer death for both men and women. This year, approximately 169,500 new cases of lung cancer are expected to be diagnosed and approximately 157,400 Americans are expected to die due to the disease. More people die of lung cancer than of colon, breast and prostate cancers combined. Non-small cell lung cancer is the most prevalent form of lung cancer, accounting for approximately 75 percent of lung cancer diagnoses in the United States. LY900003 (ISIS 3521) inhibits the production of one particular isotype, the alpha isotype, of protein kinase C, or PKC. PKC isotypes are associated with both normal and abnormal cell growth. In the laboratory, we have been able to specifically inhibit the production of the PKC-alpha isotype without inhibiting the production of other isotypes, thus allowing the inhibition of an isotype believed to be involved in abnormal cell growth without more broadly affecting the PKC isotypes.

In January 2002, we completed enrollment of a 600 patient Phase III clinical trial of LY900003 (ISIS 3521) in patients with late stage non-small cell lung cancer, which we initiated in late 2000 based on promising results in patients in the Phase II trial. Results from our Phase II trial showed a median survival of 15.9 months in patients using our drug in combination with standard chemotherapy. The typical median survival of these patients receiving standard chemotherapy alone for advanced non-small cell lung cancer is approximately seven or eight months. In addition, patients treated in our Phase II study reported no serious side effects attributable to LY900003 (ISIS 3521). Lilly also plans to conduct a Phase III clinical trial in patients with non-small cell lung cancer.

If we and Lilly determine that the data from our Phase III trial are sufficiently positive to support a single study New Drug Application, or NDA, Lilly and we plan to file the NDA in 2003. If we and Lilly determine that two Phase III studies are required, Lilly and we plan to file the NDA in 2004 with data from both our Phase III trial and Lilly's Phase III trial. LY900003 (ISIS 3521) has received fast track status from the FDA, which means that the FDA has committed to prioritizing reviews of materials related to LY900003 (ISIS 3521) prior to submission of the NDA.

In addition to the clinical trials in which we have studied LY900003 (ISIS 3521), Lilly also plans to study LY900003 (ISIS 3521) in multiple cancer indications and in combination with other chemotherapy regimens.

In Phase I and Phase II studies, LY900003 (ISIS 3521) reduced tumor mass and/or reduced tumor markers in patients with ovarian cancer and lymphoma, and stabilized disease in a patient with lung cancer. These results included complete remissions in two patients with low grade non-Hodgkin's lymphoma, a disease for which Phase II trials are in progress. Patients in prior trials of LY900003 (ISIS 3521) reported no serious side effects.

ISIS 2503—Substantial evidence exists supporting a direct role for *ras* gene products in the development and maintenance of human cancer. *Ras* proteins are involved in passing information between cells. *Ras*, in both normal and mutated forms, is associated with abnormal cell growth and, as such, is associated with cancer. ISIS 2503, a potent selective inhibitor of Harvey *ras*, or H *ras*, has been shown to inhibit abnormal cell growth in cell culture and animal models.

In Phase I studies, patients tolerated ISIS 2503 well and reported no serious side effects. We also observed evidence of activity. These results provided a basis for continuing development of ISIS 2503 in Phase II trials. In Phase II trials of ISIS 2503, we are evaluating the compound both alone and in combination with traditional cancer chemotherapies in patients with pancreatic, breast and lung cancer. We expect to present data from a number of these studies during the period ranging from late 2002 to mid 2003. Based on that data, we expect to make a decision on whether to continue into Phase III trials with ISIS 2503.

OGX-011—OGX-011 is a second-generation antisense inhibitor of clusterin, which we are co-developing and commercializing with OncoGenex Technologies Inc., a Canadian oncology-focused research and development company. OGX-011 is designed to inhibit the secretory protein clusterin, which acts as a cell-survival protein that is over-expressed in response to tumor killing strategies, such as chemotherapy, hormone ablation and radiation therapy. Based on analysis of human tumor tissue, clusterin is over-expressed in several cancers, including prostate, renal, bladder, lung and ovarian. Inhibiting clusterin is intended to enhance the effects of drug therapies in the treatment of these cancers.

In preclinical animal studies, scientists from both OncoGenex and Isis demonstrated OGX-011 improved the potency of traditional chemotherapies more than 10-fold in prostate cancer, without compromising safety. OGX-011 has also been shown to reduce levels of clusterin, as well as significantly delaying disease progression in prostate and renal cell cancer models in animals. These findings support the continued development of OGX-011 in combination with standard chemotherapy and other agents.

We expect to begin Phase I trials with OGX-011 later this year, which will make it the first antisense drug based on our proprietary second-generation chemistry to enter the clinic for the treatment of cancer. Second-generation antisense drugs offer greater potency, enhanced tolerability via subcutaneous injection, and improved dosing convenience compared to our first-generation antisense drugs.

ISIS 23722—We have identified a second-generation antisense inhibitor of survivin that we will likely develop broadly for cancer. Survivin is one of the most abundantly expressed proteins in cancers. We are in the process of determining our development plan for this new drug.

Inflammatory Diseases

Our research and development efforts in the therapeutic area of inflammatory diseases focuses on identifying and developing antisense inhibitors to proteins, such as ICAM-1 and tumor necrosis factor-alpha, or TNF-alpha. Researchers believe that these proteins are involved in inflammatory diseases. ICAM-1 is a member of the intercellular adhesion molecule family. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, such as rheumatoid arthritis, asthma, psoriasis and inflammatory bowel diseases. Experts believe that ICAM-1 contributes to the pathology of these diseases and conditions. TNF-alpha is a naturally occurring cytokine that is implicated in the development and progression of many inflammatory, infectious and autoimmune diseases. We are developing antisense drugs that inhibit the expression of TNF-alpha in multiple models of inflammatory diseases, such as rheumatoid arthritis and psoriasis. We have also identified lead compounds for other adhesion molecules including CD49d, or VLA-4.

ISIS 2302—ISIS 2302, the most advanced compound in our cell adhesion program, selectively inhibits ICAM-1 gene expression. We conducted multiple Phase II trials of ISIS 2302 in diseases such as Crohn's disease, psoriasis and ulcerative colitis.

- ***Crohn's disease***—Crohn's disease is a serious inflammatory disease that affects the entire digestive tract. A patient with Crohn's disease suffers chronic and often severe episodes of diarrhea, abdominal pain, rectal bleeding and fever. Crohn's disease afflicts approximately 400,000 people in North America and a similar number in Europe.

  In November 2001, we initiated patient enrollment in a Phase III trial of ISIS 2302 in people with active Crohn's disease. The study will evaluate the safety and efficacy of ISIS 2302 at doses higher than previously studied in controlled trials. In late 1999, we completed a 300 patient pivotal trial of ISIS 2302 in Crohn's disease, which we initiated based on positive results from a Phase II trial. In December 1999, we announced that the initial analysis of the

  data from this trial did not show efficacy and that, as a result, the data did not support an NDA filing. However, further analysis of the data indicated that those patients who received higher exposure to ISIS 2302 were more likely to experience complete clinical remission of their disease, which was the primary endpoint of the pivotal trial. The current Phase III trial is a response to this additional analysis. We expect to continue patient enrollment in this trial during 2002. Assuming that enrollment progresses according to our plans, we expect to report data in late 2003. We are currently planning a second 150 patient Phase III trial, which we plan to begin in 2002.

- ***Ulcerative Colitis***—Ulcerative Colitis, or UC, is an inflammatory disease of the colon, a part of the large intestine, which is characterized by inflammation and ulceration of the innermost lining of the colon. Symptoms characteristically include diarrhea, rectal bleeding and abdominal pain. UC differs from Crohn's disease, another inflammatory bowel disease, as it affects only the colon. According to the Crohn's and Colitis Foundation of America, an estimated 500,000 Americans have UC.

  In October 2001, we reported that data from a Phase II clinical trial demonstrated that ISIS 2302 improved symptoms of patients with active distal ulcerative colitis. Patients receiving an enema formulation of ISIS 2302 experienced a dose-dependent reduction in disease activity index score, or DAI, and clinical activity index score, or CAI. The DAI and CAI are measures of the signs and symptoms that are generally present in patients with ulcerative colitis. Patients in this Phase II trial tolerated ISIS 2302 well and reported no serious side effects. We are planning a Phase II trial

that will compare ISIS 2302 to an existing drug for ulcerative colitis. We expect this trial to begin in 2002. We are also considering another Phase II trial to evaluate dose and schedule regimens.

- ***Psoriasis***—Psoriasis is an uncomfortable, disfiguring and incurable skin disorder in which recurrent skin lesions can involve up to 80-90 percent of the body surface. The National Psoriasis Foundation estimates that more than seven million Americans have psoriasis, with more than 150,000 new cases diagnosed each year. We believe that a conveniently dosed topical cream formulation that is safe and effective would represent a significant improvement in treatment for patients and a significant commercial opportunity.

  In February 2002, we reported that in a Phase II clinical trial of patients with mild to moderate plaque psoriasis, a topical cream formulation of ISIS 2302 demonstrated a statistically significant improvement in the disease as measured by improvement in plaque induration, or thickness, and by the Investigators Global Assessment Score, which is based on a subjective zero to five point scale of disease improvement. ISIS 2302 drug concentrations observed in skin biopsies also correlated with dose regimen, supporting the potential of antisense topical drugs to treat diseases of the skin. There were no significant side effects observed in the trial. These results support the results from an earlier trial. We are considering future trials to evaluate ISIS 2302 in combination with other psoriatic medications or in other skin diseases, such as atopic dermatitis, as part of our drug discovery and development program in dermatology.

ISIS 104838—ISIS 104838 is a second-generation antisense inhibitor of TNF-alpha and our first product from our proprietary second-generation chemistry to enter the clinic. TNF-alpha, or tumor necrosis factor alpha, is a naturally occurring cytokine that is implicated in the development and progression of many inflammatory, infectious and autoimmune diseases, including rheumatoid arthritis. TNF-alpha stimulates bone and cartilage to be absorbed, facilitates inflammation and inhibits bone formation. High levels of TNF-alpha are present in patients with rheumatoid arthritis.

- ***Rheumatoid Arthritis***—According to the Arthritis Foundation, rheumatoid arthritis affects 2.1 million Americans, mostly women. Rheumatoid arthritis is a systemic disease that affects the

entire body and is one of the most common forms of arthritis. Rheumatoid arthritis is characterized by the inflammation of the membrane lining in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling. The synovium can invade locally and causes damage to bone and cartilage. Inflammatory cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

In March 2002, we initiated a second Phase II trial of ISIS 104838 in patients with rheumatoid arthritis. This Phase II trial will evaluate the safety and efficacy of ISIS 104838 in rheumatoid arthritis when administered by subcutaneous injection. This trial will be the first trial to provide us with efficacy information about ISIS 104838 in rheumatoid arthritis. In general, Phase II trials progress in 18-24 months. We expect this trial to progress in a similar fashion. In November 2001, we initiated our first Phase II trial of ISIS 104838 in patients with rheumatoid arthritis. In this trial we are studying ISIS 104838 drug concentrations in blood and tissue. We are also evaluating the drug's ability to reduce TNF-alpha levels in patients. We expect to present the data from this trial in late 2002. As we reported earlier in 2001, Phase I trials of intravenous infusion and subcutaneous injection of ISIS 104838 demonstrated fewer side effects, enhanced duration of effect and improved dosing convenience compared with our first-generation drugs.

Orasense, our joint venture with Elan, is using ISIS 104838 to develop platform oral delivery technology for antisense drugs. In April 2001, Orasense initiated the first human clinical trial of oral solid formulations of ISIS 104838 in patients with rheumatoid arthritis. This oral dosing trial is the first of several studies that Orasense plans to conduct over the next year to evaluate the absorption, distribution, metabolism and elimination of ISIS 104838 in oral dosage forms. Orasense plans to conduct efficacy trials with ISIS 104838 once it has optimized the delivery system. We hope to identify a formulation suitable for Phase II efficacy trials by the end of 2002.

- ***Psoriasis***—We initiated a Phase II clinical trial of topical ISIS 104838 in patients with psoriasis in June 2001. This is the second drug from our dermatology program and our first topical second-generation drug to enter the clinic. The first topical antisense drug to enter clinical trials was ISIS 2302. We expect to have data from this trial in the first half of 2003.

ISIS 107248—ISIS 107248 is a second-generation antisense inhibitor of CD49d, or VLA-4, which we licensed to Antisense Therapeutics Limited, or ATL, in December 2001. Inhibition of VLA-4 has been demonstrated to have a positive effect in animal models of a number of inflammatory diseases such as multiple sclerosis. Under our agreement with ATL, we are responsible for completing the required preclinical studies for ISIS 107248 and for manufacturing the drug for human clinical trials at ATL's expense. ATL is responsible for undertaking the future clinical development and the commercialization of the drug. We expect to complete the preclinical package in 2002 and expect ATL to initiate a Phase I clinical trial late in 2002 or early 2003.

Metabolic Diseases

Metabolic diseases such as diabetes and obesity are diseases that affect millions of people. According to the American Diabetes Association, diabetes affects nearly 16 million people and Type 2 diabetes constitutes 90 percent of those cases. For years, pharmaceutical companies interested in diabetes research have actively pursued phosphatases, such as PTP-1B, as part of traditional small molecule drug discovery efforts. However, due to structural similarities among closely related enzymes, it is often difficult to identify small molecule drugs with the degree of specificity that the antisense approach can obtain.

ISIS 113715—ISIS 113715, which we licensed to Merck in May 2001, is a second-generation antisense inhibitor of the PTP-1B gene for Type 2 diabetes. The preclinical data demonstrate compelling activity in multiple diabetic animal models. The preclinical data for ISIS 113715 suggests activity as an insulin sensitizer without causing hypoglycemia and while reducing cholesterol and weight gain. Under the license agreement, Merck has the right to undertake all future development of this candidate.

ISIS 13650—ISIS 13650 is an inhibitor of c-*raf* kinase for diabetic retinopathy and age-related macular degeneration. ISIS 13650 is also a second-generation product in preclinical development. We plan to initiate a Phase I clinical trial for ISIS 13650 late this year or early next year.

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 Ibis division is focused on advancing anti-infective drug discovery and diagnostics.

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 and small molecule drug discovery programs focused on various anti-viral and anti-bacterial targets, inflammatory disease targets, and other key molecular targets that might play critical roles in cancer and metabolic diseases such as diabetes and obesity.

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, we can obtain funding, expand existing programs, learn of new technologies, and gain additional expertise in developing and marketing products.

2001 Business Development Highlights

In 2001, we completed 17 transactions with 13 pharmaceutical and biotechnology partners including licenses of antisense drugs, extensions of collaborations, milestone achievements, the initiation of new antisense research and development programs, the addition of new GeneTrove customers, and licenses of intellectual property. These transactions span all four areas of our business, antisense drug discovery and development, GeneTrove, Ibis and our intellectual property estate. Following is a list of our business development highlights for 2001:

- Initiation of a broad strategic relationship with Lilly
- Licensing of our preclinical Type II diabetes antisense drug candidate, ISIS 113715, to Merck
- Licensing of our preclinical antisense drug candidate, ISIS 107248, to ATL
- Licensing of our preclinical antisense drug candidate for prostate cancer, OGX-011, to OncoGenex
- Initiation of a drug discovery collaboration with Amgen

- Addition of new GeneTrove partnerships with Amgen, Celera, and Chiron
- Initiation by our Ibis division of a new biological warfare defense research program with DARPA
- Achievement of two milestone payments for the progress our Ibis division made in its collaboration with Pfizer
- Achievement of a milestone payment for our progress in our Hepatitis C drug discovery collaboration with Merck

Eli Lilly and Company

In August 2001, we entered into a broad strategic relationship with Lilly that has four key components:

- Lilly purchased $75 million of our common stock at $18 per share.
- We licensed to Lilly rights to LY900003 (ISIS 3521), our antisense drug in Phase III trials for the treatment of non-small cell lung cancer.
- We initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related GeneTrove collaboration to determine the function of up to 1,000 genes.
- Lilly committed to lend us, interest-free, up to $100 million over a four-year period to fund our obligations under the drug discovery collaboration. This loan is repayable at our option in either cash or our common stock, valued at $40 per share.

Lilly has committed more than $200 million in funding to us over a four-year period, which consists of the $75 million equity investment Lilly made in us, the $25 million Lilly paid to us in an up-front license fee for LY900003 (ISIS 3521), the amount Lilly has committed to pay us for the remaining development and registration costs for LY900003 (ISIS 3521) and the $100 million Lilly has committed to loan us. Assuming success of LY900003 (ISIS 3521) and the success of multiple products from the collaboration, the cumulative contingent funds over the life of the development process have the potential to exceed these committed funds.

Antisense Drug Discovery Collaborations

Amgen Inc.

In December 2001, we entered into a three-year collaboration with Amgen to discover new antisense drugs. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration. If drugs from the collaboration are successful, we will receive milestone payments upon key clinical and commercial achievements, as well as royalties on sales of any products resulting from the collaboration.

Merck & Co., Inc.

In February 2001, we extended a research collaboration with Merck, which we originally entered into in June 1998, to discover small molecule drug candidates to treat patients infected with HCV. Our chemists are working together with Merck scientists to design, synthesize and evaluate novel compounds that Merck will screen in its proprietary enzymatic assays for identifying Hepatitis C virus replication inhibitors. Merck has the right to commercialize any drugs arising from the collaboration, and we retain the right to use technology developed in the collaboration in our antisense program. The collaboration provides us with annual research support plus a technology access fee, milestone

payments and royalties upon commercialization. In October 2001, we earned a $1.5 million milestone payment for progress in this collaboration.

Antisense Drug Development Collaborations

An important aspect of our business model is to selectively extend our expertise and intellectual property position in antisense technology to industry partners that are interested in developing antisense therapeutics. In return for providing companies with access to our technology, we receive an ownership interest in the resulting products and/or in the companies. 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. In 2001, we furthered this integral component of our strategy through our partnerships with major pharmaceutical companies and with OncoGenex and Antisense Therapeutics Limited. Our partnerships with OncoGenex and ATL represent our ability to broaden the reach of antisense technology in emerging companies globally. We believe we will have more such opportunities that, when combined with our own antisense drug pipeline, will allow us to participate in the establishment of a new sector of the pharmaceutical industry based on antisense technology.

Antisense Therapeutics Limited

In December 2001, we licensed ISIS 107248, which has been demonstrated to have positive effects in animal models for the treatment of certain inflammatory diseases such as multiple sclerosis, to Antisense Therapeutics Limited, an Australian company. Under the agreement, we have responsibility for completing the required preclinical studies for ISIS 107248 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 addition, we will participate with ATL in a five-year antisense drug discovery and development collaboration. ATL will pay us for access to our antisense expertise and for research and manufacturing services conducted during the collaboration. Additionally, ATL is obligated to pay us royalties on any antisense drugs discovered and developed within the partnership. In December 2001, ATL successfully completed its initial public offering in Australia. We currently own 14% of ATL's equity and hold options for additional shares.

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, an anti-cancer antisense drug candidate. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target, clusterin, with our proprietary second-generation antisense chemistry. Under the agreement, we will conduct preclinical toxicology and pharmacokinetic studies of OGX-011. We will also manufacture OGX-011 for preclinical and Phase I/II studies. OncoGenex has responsibility to perform Phase I/II clinical trials to assess the safety and efficacy of OGX-011 as a single agent and in combination with standard chemotherapy in men with localized and hormone refractory prostate cancer. We expect to begin Phase I trials with OGX-011 later this year.

Merck & Co., Inc.

In May 2001, we licensed to Merck our preclinical antisense drug candidate, ISIS 113715. ISIS 113715 is currently in preclinical development for adult onset, or Type 2, diabetes. Under the agreement, Merck has the right to undertake the development and commercialization of ISIS 113715 in exchange for an upfront fee and milestone payments and royalties to us upon its successful development and approval.

Pantheco

In September 2000, we entered into an agreement to license our novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Pantheco, on a nonexclusive basis to treat diabetes and cardiovascular diseases. On October 18, 2000, Pantheco completed a financing to raise funds to support its current business and to fund its expansion of therapeutic focus. Subsequent to the completion of Pantheco's financing, we received, as a fee for this license, nine million DKK, or $1.1 million, which was paid in Pantheco shares. In addition, Pantheco agreed to pay us royalties and milestones on any products developed using PNA. This is the second license of PNA technology from us to Pantheco. As part of the first licensing transaction completed in November 1998, we received an equity position in Pantheco. We currently own 18% of Pantheco's outstanding shares.

Elan—HepaSense—Hepatitis C

In January 2000, we formed a joint venture with Elan, HepaSense, to develop an antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus or HCV. We are currently the majority shareholder in HepaSense. HepaSense plans to develop and commercialize this novel therapeutic for HCV. HepaSense also plans to investigate delivery of ISIS 14803 with Elan's proprietary MEDIPAD Drug Delivery System, a disposable subcutaneous infusion device. We are currently conducting Phase II trials with ISIS 14803. Elan and we have each licensed significant technology to HepaSense. As part of the transaction, Elan purchased $7.5 million of our common stock at a premium to its market price. Elan may purchase an additional $7.5 million of our common stock at a premium to its market price upon completion of a mutually agreed milestone. Elan also purchased our Series B preferred stock which is convertible in the future into either our stock or stock in HepaSense. As part of the transaction, we also issued warrants to Elan, which have a five year life expiring in January 2005. In addition, Elan made available to us a $12.0 million line of credit that we may use to provide funding to HepaSense, subject to Elan's agreement.

Elan—Orasense—Oral Formulation

In April 1999, we formed a joint venture with Elan, Orasense, to develop a platform technology for the oral delivery of antisense drugs. We are currently the majority shareholder in Orasense. The first oral drug Orasense is working on is ISIS 104838, our antisense inhibitor for TNF-alpha. TNF-alpha is a gene that has been implicated in a wide range of inflammatory diseases. As part of the agreement, Elan made a $27 million equity investment in us, consisting of the purchase

of $15 million of our common stock purchased at a premium to its market price and the purchase of $12 million of convertible exchangeable preferred stock. Elan also received warrants which have a five year life expiring in April 2004. Elan has the right to convert the preferred stock into either an increased ownership interest in us or in Orasense. As part of the agreement, Elan made available to us an $18.4 million line of credit that we may use to provide funding to Orasense, subject to Elan's agreement.

We have made substantial progress in oral formulations of antisense drugs, achieving significant oral bioavailability by combining novel chemistries and formulation approaches. Elan, a world leader in oral drug delivery technology, has demonstrated the oral delivery and bioavailability of large macromolecules with properties similar to many antisense drugs. Both companies are combining existing technologies and expertise with new research efforts toward the goal of building a proprietary platform technology for the oral delivery of antisense drugs. Orasense is currently conducting Phase I trials of oral formulations of ISIS 104838 in healthy volunteers. Orasense plans to conduct efficacy trials with ISIS 104838 once it has optimized the delivery system. We hope to select a formulation suitable for Phase II efficacy trials by the end of 2002.

Antisense Commercialization

Novartis Ophthalmics

In 1997, we entered into an agreement with Novartis Ophthalmics, formerly CIBA Vision Corporation, granting them exclusive worldwide distribution rights for Vitravene. The terms of the agreement provided for us to receive $20 million in pre-commercial fees and milestones. As of December 31, 2001, we had received the full $20 million of these pre-commercial fees and milestones. While Novartis Ophthalmics markets and sells Vitravene worldwide, we manufacture and sell Vitravene to Novartis Ophthalmics at a price that allows us to share the commercial value of the product with them. The FDA approved Vitravene for commercial marketing in August 1998. In 1999 Vitravene received marketing approval in Europe and Brazil. Vitravene has also been approved for marketing in Australia. We delivered our first commercial shipment of Vitravene to Novartis Ophthalmics in August 1998.

GeneTrove Collaborations

Pharmacia Corporation

In March 2002, we initiated a functional genomics collaboration with Pharmacia. Under the terms of the agreement, we are performing gene functionalization and target validation services to help Pharmacia validate and prioritize genes for its drug discovery program. As part of the collaboration, we also granted Pharmacia a license to specific patents covering the Ribonuclease H, or Rnase H, mechanism of action for its in-house antisense based functional genomics program.

Merck & Co., Inc.

In February 2002, we initiated a functional genomics collaboration with Merck. Under the agreement, we are performing gene functionalization and target validation services to help Merck validate and prioritize genes for its drug discovery program.

Amgen Inc.

In December 2001, we initiated a functional genomics collaboration with Amgen. Under the terms of the agreement, we are performing gene functionalization and target validation services to help Amgen validate and prioritize genes for its drug discovery program. As part of the collaboration, we also granted Amgen a license to specific patents covering the Ribonuclease H, or Rnase H, mechanism of action for its in-house antisense based functional genomics program.

Chiron Corporation

In December 2001, we initiated a functional genomics collaboration with Chiron Corporation. Under the terms of the agreement, we are performing gene functionalization and target validation services to help Chiron validate and prioritize genes for its drug discovery program. As part of the collaboration, we also granted Chiron a license to specific patents covering the Ribonuclease H, or Rnase H, mechanism of action for its in-house antisense based functional genomics program.

Celera Genomics Group

In July 2001, we entered into a collaboration with Celera to identify the biological role of more than 200 genes. Celera has the right to select for study a portfolio of genes, from which Celera can further select a limited number of genes for their exclusive use. The data for the remainder of the genes will be included in our human gene function database. We retain the rights to develop and commercialize antisense drugs to genes in the collaboration. Celera has agreed to pay us fees for this 18-month collaboration.

Abbott Laboratories, Inc.

In December 2000, we extended our target validation collaboration with Abbott, which began in December 1998, for an additional two years. Through the collaboration, we are utilizing our target validation technology to enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Under the agreement, Abbott agreed to pay us an up-front fee, research fees, milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. We also received rights to develop drugs for Abbott targeting Abbott proprietary genes.

Johnson & Johnson Pharmaceutical Research & Development

In July 2000, we initiated a target validation agreement with R.W. Johnson Pharmaceutical Research Institute, a division of Ortho-McNeil Pharmaceutical, Inc. This agreement was subsequently assigned to Johnson & Johnson Pharmaceutical Research & Development, LLC, or J&JPRD. Under the agreement, we are using our proprietary target validation technology to assess and prioritize genes identified by J&JPRD. This collaboration may enable J&JPRD to determine the function and therapeutic value of novel gene targets. It also provides us with information on these targets to assist in our development of novel antisense drugs. The initial term of this collaboration is for one year after the shipment of the last antisense inhibitor.

Aventis

In September 1999, we entered into a target validation collaboration with Aventis. Through the collaboration, we are using our target validation technology to assess genes identified within Aventis' genomics programs. This collaboration enables Aventis to determine the function and therapeutic value of numerous novel gene targets and to potentially use this information about gene function to develop pharmaceutical products. It also provides us with valuable information on these targets to assist in our development of novel antisense drugs. The initial term of this collaboration is three years with certain provisions for early termination or extension of the collaboration. Under the terms of the agreement, Aventis will pay us research fees and milestone payments based on the success of the program.

Ibis Collaborations

DARPA

In October 2001, our Ibis division received a multi-year contract with the Defense Advanced Research Projects Agency, or DARPA, to develop a sensor to detect infectious agents used in biological warfare attacks. We expect to receive funding of up to $8.9 million for the research program Triangulation Identification Genetic Evaluation of biological Risks, or TIGER. Over the past year, San Diego-based Science Applications International Corporation, or SAIC, and Ibis have worked together to receive the TIGER program award. The SAIC and Ibis partnership combines Ibis' expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal processing capabilities.

The TIGER contract builds on the biological warfare countermeasure research Ibis has conducted in two previous DARPA programs. The preceding studies, initiated in 1997 and 1999, focused on creating a strategy to identify common binding sites, or structured regions with RNA, to a wide range of infectious agents in order to develop small molecules to combat infectious pathogens. Ibis' work for DARPA has yielded a number of proprietary targets and significant advances in RNA-targeted drug design.

Agouron Pharmaceuticals, Inc., a Pfizer company

In June 2000, our Ibis division and Pfizer, entered into a collaboration for the discovery and development of small molecule drugs against certain RNA targets. Using Ibis' proprietary technology and Pfizer's expertise in small molecule drug discovery, the collaboration focuses on discovering drugs that bind to RNA. Pfizer agreed to fund collaborative research, pay an up-front technology access fee and make milestone payments. In addition, under the terms of the agreement, Pfizer agreed to develop and commercialize drugs discovered through the collaboration. Also, Pfizer agreed to pay us royalties on sales of any drugs resulting from the collaboration. In May 2001 and October 2001, Ibis earned a $2.5 million milestone payment and a $1.5 million milestone payment, respectively, for progress in this collaboration. This collaboration is scheduled to end in June 2002.

Intellectual Property Licensing Agreements

In Licensing Arrangements

Integrated DNA Technologies, Inc.

In December 2001, we established a long-term research-scale antisense inhibitor supply agreement with Integrated DNA Technologies, Inc., or IDT. IDT is a leading supplier of antisense inhibitors used in research. Additionally, we further solidified our intellectual property leadership position in antisense technology by broadening our license to certain antisense patents from IDT.

In the long-term supply agreement we have initiated with IDT, IDT agreed to manufacture research-scale antisense inhibitors and research reagents to our specifications. The agreement enables us to meet increasing demand for functional genomics services that our GeneTrove division provides to a growing number of major pharmaceutical and biotechnology customers. We paid IDT $5 million toward our future purchase of antisense inhibitors.

Consistent with our goal of broad control of intellectual property associated with antisense technology, we have expanded our existing licensing agreement with IDT on certain patents, which are useful in functional genomics and in making certain antisense drugs. The expanded license allows us to exclusively sublicense this intellectual property for functional genomics purposes. The agreement also eliminates prior milestone payment obligations and significantly reduces royalty rates associated with commercialized second-generation antisense drugs. We paid IDT $3.5 million in 2001 and will pay IDT $1.4 million over the next four years for the license.

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 will 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, under this agreement.

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 provides 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 million.

Out Licensing Arrangements

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech Pharmaceuticals, Inc., a privately held company, certain of our patents necessary for Eyetech to develop, make and commercialize EYE001, a non-antisense compound intended for use in the treatment of ophthalmic diseases. EYE001 is currently in Phase II/III clinical trials sponsored by Eyetech. Upon signing of the licensing agreement Eyetech paid us an 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.

Roche Molecular Systems

In October 2000, we completed the licensing of 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 certain of our proprietary chemistries, in exchange for initial and ongoing payments from Roche to us.

Manufacturing

In the past, production of chemically modified oligonucleotides, like those used in our research and development programs, was generally expensive and difficult, except in small quantities. As a result, we have dedicated significant resources to focus on ways to improve manufacturing capacity. Because all oligonucleotide compounds are made of variants of the same nucleotide building blocks and are produced using the same types of equipment, we found that the same techniques used to efficiently manufacture one oligonucleotide drug product proved helpful in improving the manufacturing processes for many other oligonucleotide products. Through the development of several proprietary chemical processes for scaling up manufacturing capabilities, we have been able to greatly reduce the cost of producing oligonucleotide compounds. For example, we have significantly reduced the cost of raw materials, while at the same time increasing our capacity to make the compounds. We have both internal programs and outside collaborations with various industry vendors to allow for even greater production capacity.

We have contractual obligations to manufacture clinical trial materials and/or commercial supply for Amgen, ATL, Lilly, Merck, Novartis, OncoGenex and for our two joint ventures with Elan, HepaSense and Orasense. We have a 12,000 square foot Good Manufacturing Practices manufacturing facility located in Carlsbad, California. We believe we have sufficient manufacturing capacity to meet both current and future research and clinical needs both for ourselves and for our partners. We also believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated commercial needs. We also believe that with reasonably anticipated benefits from increases in scale, 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 February 28, 2002, we own or have exclusively licensed nearly 900 issued

patents worldwide. Patents issued to us, applied for by us or exclusively licensed by us cover the following types of inventions, processes and products:

- Methods claims for the use of RNA/DNA oligonucleotides, or 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 oligonucleotide structures, 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 inhibit expression of the target gene;
- 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, or SAR by mass spectrometer; and
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Methods claims for rapidly discovering antisense oligonucleotides, which cover our rapid through-put method of discovering antisense oligonucleotides.

On July 9, 2001, we filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999. In response to this suit, Sequitur has filed certain counterclaims. We believe that we have meritorious defenses to all of these counterclaims. On December 12, 2001, we filed a second suit against Sequitur, Inc. in the U.S. District Court for the Southern District of California. The suit alleges infringement of U.S. Patent No. 6,326,199 entitled "Gapped 2' Modified Oligonucleotide", which was issued to us on December 4, 2001. Sequitur has answered but not filed any counterclaims.

Government Regulation

Our manufacture and potential sale of therapeutics are subject to extensive regulation by United States and foreign governmental authorities. 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. Pharmaceutical manufacturing facilities are also regulated by state, local and other authorities.

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.

Competition

For many of their applications, antisense-based drugs as well as Ibis small molecules will be competing with existing therapies for market share. In addition, a number of companies are pursuing the development of oligonucleotide-based technology and the development of pharmaceuticals utilizing such technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies. Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and may be better equipped to develop, manufacture and market products. In addition, many of these companies have extensive experience in preclinical testing and human clinical trials. These companies may develop and introduce products and processes competitive with or superior to ours. Furthermore, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection and may establish collaborative arrangements for product and clinical development in the areas of our business.

Vitravene and our other products under development address numerous markets. Our competition has been and will continue to be determined in part by the diseases for which our compounds are developed and may ultimately be approved by regulatory authorities. 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 that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price and patent position.

Over the past several years, the market for Vitravene, our antisense drug for CMV retinitis, has been affected by a number of factors. The introduction of new anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, has prolonged survival in HIV-infected individuals. Over the last several years, this has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections including CMV retinitis. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet, cidofovir and fomivirsen, or Vitravene. Foscarnet and cidofovir are available in intravenous dosing forms only. Ganciclovir is available in intravenous and oral doses, as well as in an intraocular implant form. Vitravene is administered intravitreally.

We currently have two drugs in Phase III trials. We licensed LY900003 (ISIS 3521), our antisense drug for non-small cell lung cancer, to Lilly in August 2001. Under our agreement with Lilly, Lilly is responsible for the commercialization of LY900003 (ISIS 3521). We expect that LY900003 (ISIS 3521) will be used in combination with current standard chemotherapy regimens for non-small cell lung cancer. As such, we expect that it will be complementary to existing drugs for the treatment of non-small cell lung cancer rather than directly competitive. Our second drug in Phase III trials is ISIS 2302, which we are studying in patients with Crohn's disease. ISIS 2302 will likely compete with Johnson & Johnson's drug, Remicade, which is approved for the treatment of Crohn's disease and rheumatoid arthritis.

Our competitive position also depends upon our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary products or processes and secure sufficient capital resources for the substantial period between technological conception and commercial sales.

Employees

As of February 28, 2002, we employed 434 individuals, of whom 171 hold advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. None of our employees is covered by collective bargaining agreements, and management considers relations with its employees to be good.

Executive Officers

The following set forth certain information regarding our executive officers as of February 28, 2002:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	56	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, Esq.	46	Director, Executive Vice President, Chief Financial Officer, and Secretary
C. Frank Bennett, Ph.D.	45	Vice President, Antisense Research
Richard K. Brown, Ph.D.	49	Isis Vice President and President, GeneTrove
Douglas L. Cole, Ph.D.	54	Vice President, Development Chemistry and Pharmaceutics
F. Andrew Dorr, M.D.	48	Vice President, Clinical Research and Chief Medical Officer
David J. Ecker, Ph.D.	48	Isis Vice President and President, Ibis Therapeutics
Arthur A. Levin, Ph.D.	48	Vice President, Toxicology and Pharmacokinetics
Patricia Lowenstam	55	Vice President, Human Resources and Operations
Karen Lundstedt	37	Vice President, Corporate Communications
John McNeil	37	Vice President, Informatics

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. Dr. Crooke is Chairman of the Board of Idun Pharmaceuticals, Inc. He also serves as a director of Valentis, Inc., SYNSORB Biotech Inc., EPIX Medical, Inc. and Antisense Therapeutics Limited. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

B. LYNNE PARSHALL, ESQ.
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 Visitors at Stanford University Law School. Ms. Parshall is also a member of the Licensing Executives Society and a member of the American, California and San Diego bar associations.

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

Dr. Bennett has served as our Vice President, Biology 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.
Isis Vice President and President, GeneTrove

Dr. Brown has served as our President of GeneTrove since June 2001. Prior to joining GeneTrove, 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.

DOUGLAS L. COLE, PH.D.
Vice President, Development Chemistry and Pharmaceutics

Dr. Cole has served as our Vice President, Development Chemistry and Pharmaceutics since January 1995. From January 1993 until January 1995, he was our Executive Director, Development Chemistry and Pharmaceutics and from October 1991 until January 1993, he was a Director in our Development Chemistry department. Prior to joining Isis in 1991, Dr. Cole was Director of Chemical Affairs for Marion Laboratories.

F. ANDREW DORR, M.D.
Vice President, Clinical Research and Chief Medical Officer

Dr. Dorr, a medical oncologist, has served as our Vice President, Clinical Development and Chief Medical Officer since August 2000. From June 1996 until August 2000, Dr. Dorr was our Vice President, Clinical Development. Prior to joining Isis in June 1996, Dr. Dorr worked for Eli Lilly and Company where he was the Medical Research Advisor for strategic planning and implementation of cancer drug development.

DAVID J. ECKER, PH.D.
Isis Vice President and President, Ibis Therapeutics

Dr. Ecker was a founder of the Company and has served as our Vice President & Managing Director of Ibis Therapeutics, a division of Isis Pharmaceuticals, since June 1995. In 2001 he assumed the role of President of the 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, Toxicology and Pharmacokinetics

Dr. Levin, a toxicologist, has served as our Vice President, Toxicology and Pharmacokinetics since January 1998. From August 1996 to January 1998, Dr. Levin was our Executive Director, Toxicology and Pharmacokinetics. Dr. Levin joined Isis in February 1995 as a Director in our Toxicology department and served in that capacity until August 1996. Prior to joining Isis in 1995, Dr. Levin worked for Hoffmann-La Roche Inc. where he was Research Leader in their Investigative Toxicology Department.

PATRICIA LOWENSTAM
Vice President, Human Resources and Operations

Ms. Lowenstam has served as our Vice President, Human Resources 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, Zales Jewelers, and the May Company.

KAREN LUNDSTEDT
Vice President, Corporate Communications

Ms. Lundstedt has served as our Vice President, Investor Relations and Corporate Communications since April 2000. Ms. Lundstedt joined Isis in August 1999 as our Executive Director, Investor Relations and Corporate Communications. From September 1991 until joining Isis, Ms. Lundstedt held various management positions at Dura Pharmaceuticals, a specialty respiratory pharmaceutical and pulmonary drug delivery company.

JOHN MCNEIL
Vice President, Informatics

Mr. McNeil, has served as our Vice President of Informatics since October 1999; in November 2001 he became one of our executive officers. Mr. McNeil joined Isis in October 1997 as our Director, Informatics and served in that capacity until October 1999. Prior to joining Isis, Mr. McNeil was founder and President of John McNeil & Co., Inc., and held various positions at SAIC in San Diego from 1989 to 1997.

RISK FACTORS

Investing in our common stock involves a high degree of risk. In addition to the other information in this Annual Report on Form 10-K, you should carefully consider the risks described below before purchasing our common stock. 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 common stock could decline, and investors in our common stock might lose all or part of their investment.

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 U.S. 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 such receipt 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 could have a similar negative impact.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, be approved for commercialization or will be successfully commercialized by us or our partners.

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 such 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, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. Most of our resources are being applied 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, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

If our products are not accepted by the market, we are not likely to generate significant 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 any of our products in development, if approved for commercialization, will be used by doctors to treat patients. We currently have one commercially available product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small market. We and our partners may not be successful in commercializing 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 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 are unable to obtain additional partners, progress on our drug development programs could be delayed or stop.

We have entered into collaborative arrangements with third parties to develop certain 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; 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 be negatively affected. 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. Our most advanced drug candidate, LY900003 (ISIS 3521), is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, Elan Corporation, plc, Merck & Co., Inc. and OncoGenex Technologies Inc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

Historically, 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.

If our GeneTrove business is unable to market its products and services as planned, we could lose our investment in this technology.

Our business could suffer if pharmaceutical companies do not use our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and gene functionalization service business for validation and functionalization of gene targets for drug discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance. In addition, if customers do not subscribe to the database at the level we have planned, our GeneTrove business could fail to make the planned contribution to our financial performance.

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

Because drug discovery and development and the development of database products and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of December 31, 2001, our accumulated losses were approximately $387 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. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales

potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

Most 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, we believe that our available cash, cash equivalents and short-term investments at December 31, 2001 combined with investment income and committed contractual cash payments, will be sufficient to meet our anticipated requirements for at least the next 36 months. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of our proprietary technologies, we may 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 these 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 the marketing of our gene function database and research service products; 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 additional funds are raised

by issuing equity securities, the shares of existing stockholders will be diluted and their price may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may 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. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited 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 are enforced by the FDA 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.

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. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

Our GeneTrove division competes with others in the use of antisense technology for gene target validation and gene functionalization, as well as with other technologies useful for target validation and gene functionalization. Our competition may provide services having more value to potential customers or may market their services more effectively to potential customers. In either case, our gene functionalization and target validation businesses may not contribute to our financial performance as planned.

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 are unable to protect our patents or our proprietary rights, others may be able to compete more directly against us.

Our success depends to a significant degree upon our ability to develop and secure intellectual property rights to proprietary products and services. However, patents may not be granted 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.

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 litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging patent infringement. On December 12, 2001, we initiated a second action against Sequitur, inc. alleging patent infringement. If we do not prevail in the defense of these patents, it could impact our ability to realize future licensing revenues.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we might be forced 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, our stock price could decrease.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter the clinic, when a clinical trial will be completed or when an application for marketing approval will be filed. Some of our estimates are included in this Annual Report on Form 10-K. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and our stock price 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 management. 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. Our

collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

Our stock price may continue to be highly volatile, which could make it harder for investors to liquidate their investment in our common stock and could increase their 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. During the twelve months preceding December 31, 2001, the market price of our common stock ranged from $7.88 to $27.15 per share. The market price can be affected by many factors, 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 $66^2/_3\%$ 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, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the chief executive officer. 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 some of our other 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.

ITEM 2. Properties

We occupy approximately 180,600 square feet of laboratory and office space, including a 12,000 square foot Good Manufacturing Practices manufacturing suite, in five buildings located on our "campus" in Carlsbad, California. We own three of these buildings and, as of December 31, 2001, these buildings secured approximately $7 million of our debt. We lease two of the buildings under lease agreements expiring in 2007 and 2010. In January 2002, we entered into a lease,

which expires in July 2007, where we secured an additional 37,400 square feet of space in Carlsbad, California. We are constructing improvements to this space so that we may use it for offices.

ITEM 3. Legal Proceedings

On July 9, 2001, we filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999. In response to this suit, Sequitur has filed certain counterclaims. We believe that we have meritorious defenses to all of these counterclaims. On December 12, 2001, we filed a second suit against Sequitur, Inc. in the U.S. District Court for the Southern District of California. The suit alleges infringement of U.S. Patent No. 6,326,199 entitled "Gapped 2' Modified Oligonucleotide", which was issued to us on December 4, 2001. Sequitur has answered but not filed any counterclaims.

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

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
2000		
First Quarter	$ 39.00	$ 5.75
Second Quarter	$ 16.25	$ 8.06
Third Quarter	$ 15.75	$ 10.50
Fourth Quarter	$ 14.75	$ 8.81
2001		
First Quarter	$ 13.00	$ 7.97
Second Quarter	$ 13.17	$ 7.88
Third Quarter	$ 18.05	$ 9.75
Fourth Quarter	$ 27.15	$ 16.70

As of February 28, 2002, there were approximately 1,046 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future. Under the terms of certain term loans, we are restricted from paying cash dividends until the loans are fully repaid.

Recent Sales of Unregistered Securities

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 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 will 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, under this agreement.

ITEM 6. Selected Financial Data (in thousands, except per share amounts)

	Years Ended December 31,				
	2001	2000	1999	1998	1997
Statement of Operations Data:					
Revenues (includes amounts for R&D, Licensing and royalties)	$ 53,273	$ 37,255	$ 33,925	$ 39,171	$ 32,722
Research and development expenses	$ 83,741	$ 57,014	$ 66,413	$ 62,200	$ 55,940
Net loss applicable to common stock	$ (75,131)	$ (54,699)	$ (59,645)	$ (42,983)	$ (31,066)
Basic and diluted net loss per share	$ (1.70)	$ (1.48)	$ (2.08)	$ (1.60)	$ (1.17)
Shares used in computing basic and diluted net loss per share	44,109	37,023	28,703	26,873	26,456

	December 31,				
	2001	2000	1999	1998	1997
Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 312,018	$ 127,262	$ 52,839	$ 58,848	$ 86,786
Working capital	$ 280,569	$ 118,568	$ 44,213	$ 40,651	$ 62,573
Total assets	$ 417,061	$ 183,256	$ 103,107	$ 96,074	$ 117,881
Long-term debt and capital lease obligations, less current portion	$ 125,710	$ 102,254	$ 87,254	$ 77,724	$ 56,452
Accumulated deficit	$ (386,591)	$ (311,460)	$ (256,761)	$ (197,116)	$ (154,133)
Stockholders' equity (deficit)	$ 223,099	$ 66,366	$ 869	$ (4,186)	$ 34,852

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 can design 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 a broad pipeline of 13 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including cancer and inflammatory, viral, metabolic and dermatological diseases, and are being studied in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

Established in 2000, GeneTrove is our functional genomics division, which commercializes the first step of our antisense drug discovery program. GeneTrove capitalizes on the specificity of antisense, using it as a tool to identify what a gene does, which is called gene functionalization, and whether a specific gene is a good target for drug discovery, which is called target validation. GeneTrove provides valuable functional genomics services to the pharmaceutical and biotechnology industry, potentially enhancing and expediting drug discovery and development decisions, and generating near-term revenue for us in the process. We have collaborations with nine major pharmaceutical partners for these services, including Abbott Laboratories, Inc.; Amgen Inc.; Aventis (Rhone-Poulenc Rorer); Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; Johnson & Johnson Pharmaceutical

Research & Development, LLC; Merck & Co., Inc. and Pharmacia Corporation. We expect these collaborations to fund the functionalization of approximately 1,400 new genes over the next two to three years. We have supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product. This database is expected to contain proprietary information about the function of thousands of genes, which we believe pharmaceutical companies will find valuable in designing and prioritizing their drug discovery programs. In addition to GeneTrove's functional genomics services and its database product, partners can license access to our functional genomics patent portfolio.

Our Ibis Therapeutics division is taking advantage of the investment we have made in RNA-based drug discovery. The division is using its proprietary technology to create small molecule drugs that bind to structured regions of RNA—areas that are not available to antisense drug discovery. RNA is an optimal target as it is universal, simple in structure and predictable. Historically, the division has focused primarily on the research and development of anti-bacterials, anti-virals and anti-fungals, but this past year Ibis expanded its program to include a diagnostic application of its technology. Since its inception, Ibis has received significant financial support from various federal government agencies to use its technology for the development of RNA-based countermeasures to biological warfare. In October 2001, Ibis received a two-year contract with the Defense Advanced Research Projects Agency, or DARPA, to develop a sensor to detect infectious agents used in biological warfare attacks. We expect to receive funding of up to $8.9 million. During 2001, Ibis earned two research milestone payments totaling $4.0 million as recognition of the division's progress in its collaboration with Agouron Pharmaceuticals, Inc., a Pfizer company.

Critical Accounting Policies

We prepare our financial statements in conformity with generally accepted accounting principles 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 estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes thereto. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when all contractual obligations have been satisfied and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments 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 obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Lilly, Antisense Therapeutics Limited, Amgen, Merck and our government contract with DARPA entered into in fiscal 2001. Additionally, licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable are recognized as revenue immediately. Licensing and royalty agreements where we have no future obligations include Eyetech Pharmaceuticals and Coley Pharmaceuticals Group entered into in 2001 and 2000, respectively.

Valuation of Intellectual Property

We evaluate our licenses and patent assets for impairment on a quarterly basis, and whenever indicators of impairment exist. During this process, we review our portfolio of 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 challenges or potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that it is determined that an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Short-Term Investments

We invest our excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends and interest rates. In determining if and when a decline in market value below amortized cost is other-than-temporary, we, together with our external portfolio managers, evaluate the market conditions, offering prices, trends of earnings, price multiples, and other key measures for our investments in debt instruments. When such a decline in value is deemed to be other-than-temporary, we recognize an impairment loss in the period operating results to the extent of the decline. To date, we have not had any material losses related to our excess cash or short-term investments.

Effects of Related Party Transactions

Eli Lilly and Company

In August 2001, we entered into a strategic alliance with Lilly in which we licensed our investigational drug, LY900003 (ISIS 3521) for non-small cell lung cancer, and formed a four-year research collaboration. As part of the agreement, Lilly paid an up-front fee of $25 million for the license, provided a $100 million interest free loan to fund the research collaboration, agreed to reimburse us for remaining Phase III development and registration costs of LY900003 (ISIS 3521), and purchased $75 million of our common stock at $18 per share. The loan is due in four years and is payable at any time in cash or our common stock at $40 per share, at our option. At December 31, 2001, Lilly owned approximately 7.75% of our outstanding common stock. Additionally, Lilly agreed to reimburse us for costs we incur related to the ongoing trials for LY900003 (ISIS 3521), including the Phase III trial.

We are recognizing the $25 million license fee as research and development revenue under collaborative agreements over the estimated period of our performance obligations. As of December 31, 2001 we had drawn down $20 million on the $100 million loan. We discounted the $20 million that had been drawn on the loan as of December 31, 2001 to its net present value by imputing interest on that amount at 20%, which represented market conditions in place at the time we enter 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, and is accounted for as deferred revenue and is recognized as revenue over the period of performance. As of December 31, 2001, the balances related to the loan in long-term obligations and long-term deferred revenue was $9.7 million, and $10.3 million, respectively.

Elan Corporation, plc, and Joint Ventures with Orasense and HepaSense

In April 1999 and January 2000 we formed joint ventures with Elan Corporation, plc, named Orasense and HepaSense, respectively. Both joint ventures are Bermuda limited companies. We and Elan provide development and manufacturing services to Orasense and HepaSense. While we own 80.1% of the outstanding common stock of each of the joint ventures, Elan and its subsidiaries have

retained significant minority investor rights that we consider "participating rights" as defined in EITF 96-16. Therefore, we do not consolidate the financial statements of Orasense or HepaSense, but instead account for our investments in Orasense and HepaSense under the equity method of accounting for investments. Additionally, Elan made available to us an $18.4 million and a $12 million line of credit for Orasense and HepaSense, respectively. Each line was put into place at the time its respective joint venture was formed and carries a 12% interest rate. For additional information regarding Orasense and HepaSense, see Notes 3, 6 and 9 of our audited financial statements.

For the years ended December 31, 2001, 2000 and 1999 we recognized $5.4 million, $5.2 million, and $4.4 million, respectively, from Orasense as research and development revenues from affiliates. Additionally, we recorded $10.3 million, $9.7 million, and $7.2 million for the years ended December 31, 2001, 2000, and 1999, respectively, as equity in net loss from affiliates. At December 31, 2001 and 2000 our balance sheet reflected $1.7 million and $968,000, respectively, under contracts receivable related to Orasense. During 2001 and 2000, we borrowed $5.6 million and $6.7 million, respectively, under this convertible debt agreement to provide development funding to Orasense. Based on the principal and accrued interest outstanding at December 31, 2001, the loan balance due at maturity will be $23.1 million, provided that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility, including accrued interest, as of December 31, 2001 and 2000 was $16.7 million and $9.7 million, respectively, which approximated fair value.

For the years ended December 31, 2001 and 2000, we recognized $5.2 million and $2.8 million, respectively, from HepaSense as research and development revenues from affiliates. Additionally, we recorded $8.3 million and $6.2 million for the years ended December 31, 2001 and 2000, respectively, as equity in net loss from affiliates. At December 31, 2001 and 2000 our balance sheet reflected $2.5 million and $481,000, respectively, under contracts receivable related to HepaSense. During 2001 and 2000, we borrowed $2.6 million and $1.8 million, respectively, under this convertible debt agreement to provide development funding to HepaSense. Based on the principal and accrued interest outstanding at December 31, 2001, the loan balance due at maturity will be $7.0 million, providing that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility, included accrued interest, as of December 31, 2001 and 2000 was $4.8 million and $1.9 million, respectively, which approximated fair value.

Results of Operations

Years Ended December 31, 2001 and December 31, 2000

Revenue

Total revenue for the year ended December 31, 2001 was $53.3 million, compared to $37.3 million for 2000. The increase of $16.0 million was primarily a result of increased research and development revenues under collaborative agreements. During 2001, we successfully completed 17 transactions with 13 partners, which served to increase our revenue. The most significant contributor was our strategic alliance with Lilly. Also contributing to the increase in total revenue was research and development revenues from affiliates, under which we reported a $2.6 million increase in 2001 from 2000. The increase in total revenue was partially offset by a decrease in revenue from licensing and royalty revenues in 2001 from that reported in 2000.

Research and Development Revenues under Collaborative Agreements

Under the category research and development revenues under collaborative agreements, for the year ended December 31, 2001, we reported $40.4 million, compared to $16.9 million for 2000. The increase of $23.5 million is a result of our entering into a variety of new partnerships, earning collaboration milestones, and licensing of our intellectual property. Contributing to a majority of the increase was revenue associated with our strategic alliance with Lilly which we entered into in

August 2001. As part of the Lilly alliance we licensed our Phase III investigational drug, LY900003 (ISIS 3521). In May 2001, we entered into an agreement with Merck in which we licensed our preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. Other sources of revenue in 2001 included: the initiation of an antisense drug discovery collaboration with Amgen; the addition of new GeneTrove partnerships with Celera, Chiron and Amgen; the initiation of a new biological warfare defense research program with DARPA; the achievement of two milestone payments for the progress our Ibis division made in its collaboration with Pfizer; and the achievement of a milestone from Merck in recognition of our progress in the hepatitis C drug discovery collaboration.

Research and Development Revenues from Affiliates

Research and development revenue from affiliates consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. During 2001, we recognized $5.4 million and $5.2 million from Orasense and HepaSense, respectively, as revenue. During 2000, we recognized $5.2 million and $2.8 million as revenue from Orasense and HepaSense, respectively. The increase of $2.6 million is a result of a full year of HepaSense activity reflected in 2001, while 2000 reflected eleven months of activity of which the first few months were during a start-up period.

Licensing and Royalty Revenues

Our revenue from licensing activities and royalties was $2.3 million for the year ended December 31, 2001, compared with $12.4 million in 2000. The primary source of the revenue reported in 2001 was our license in December 2001 of intellectual property to Eyetech Pharmaceuticals, Inc., a privately held company. Under the terms of the agreement, Eyetech agreed to pay us $2.0 million as a license fee, for which we had no obligations or services required to be performed. The decrease of $10.1 million in 2001 from that reported for 2000 is primarily related to one-time revenue recorded in 2000 associated with the sale of certain patents to Coley Pharmaceuticals Group.

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, including GeneTrove, antisense drug development, our Ibis Therapeutics' division and R&D Support costs.

For the year ended December 31, 2001, we reported total research and development expenditures of $83.7 million, compared to $57.0 million reported in 2000. The $26.7 million increase in 2001 over 2000 was primarily due to our investment in the 13 products we had in development during 2001, costs associated with increased gene functionalization and target validation activities, costs associated with our continued database development efforts and costs associated with our Lilly research collaboration. Also included in the increase were costs associated with rebuilding efforts within our antisense drug discovery group to pre-1999 levels.

Antisense Drug Discovery

The first steps in our drug discovery process are for our researchers to identify what a gene does, called gene functionalization and then to determine whether a specific gene is a good target for drug discovery, called target validation. We use this information in our internal drug discovery process and, through our GeneTrove division, we sell these services and the resulting information to pharmaceutical and biotechnology companies in collaborations such as those we have with Abbott, Aventis, Amgen, Celera, Chiron, Lilly, Johnson & Johnson, Merck and Pharmacia. GeneTrove is an integral component of our antisense drug discovery group. As such, GeneTrove shares many of its resources including people, equipment and facilities, with the rest of our antisense drug discovery group.

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 potentially can be administered orally. 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 such as 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 such as Lilly, in the areas of metabolic and inflammatory diseases, and most recently, with Amgen.

As we expand our research programs into new sites in the body and new disease categories, as we continue to identify antisense inhibitors to 10,000 human genes and as we continue to populate GeneTrove's proprietary database with information on those 10,000 genes, we would expect to see our expenses for antisense drug discovery increase. Our existing relationships with Lilly and Amgen combined with our GeneTrove collaborations help fund our many research programs as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug discovery costs for the year ended December 31, 2001 totaled $20.9 million compared to $12.5 million for 2000. The increase was principally a result of increased gene functionalization and target validation activities, continued database development and costs associated with our Lilly research collaboration.

Antisense Drug Development

Our development activities reflect our efforts to advance our pipeline drugs through the various stages of preclinical, or animal, studies and human clinical trials. The expenditures that will be necessary to execute our development plans are subject to numerous uncertainties, which may affect our research and development expenditures and capital resources. We test our potential product candidates in numerous preclinical studies to identify disease indications for which they may be candidates to begin clinical trials. Completion of clinical trials may take several years, and the length of time generally varies substantially according to the complexity, novelty and intended use of the product candidate. We estimate that the clinical trials we generally conduct are typically completed over the following timelines: Phase I—one year, Phase II—one to two years, and Phase III—two to four years. However, the duration and the cost of clinical trials may vary significantly depending on a variety of factors including a trial's protocol, the number of patients in the trial, the duration of patient follow-up, the number of clinical sites in the trial, and the length of time required to enroll suitable patient subjects. Although we spend a considerable amount of time planning our clinical trials, often we are required to alter from our plan. For example, we may need to alter the number of patients in the trial or extend the duration of patient follow-up. Any required deviation from our plan, may require us to incur additional expenditures.

We may conduct multiple clinical trials on a drug candidate including multiple clinical trials for the variety of 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. Generally, a late stage Phase III trial is substantially more expensive than early stage trials, such as Phase I or Phase II. As of December 31, 2001 we had 13 drug candidates in various stages of development. LY900003 (ISIS 3521), our most advanced product currently under development, is undergoing Phase III clinical trials for the treatment of non-small cell lung cancer. In November 2001, we initiated a Phase III trial of ISIS 2302 in patients with an inflammatory bowel disease known as Crohn's disease. Additionally, we have six products in Phase II trials, and five products in preclinical studies. 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, under our licensing

agreement with Lilly for LY900003 (ISIS 3521), we received an up-front license payment, which helped fund the costs we incurred during 2001 for our current Phase III trial. In addition, Lilly agreed to reimburse us for our costs related to the continued development of LY900003 (ISIS 3521).

Development expenditures totaled $37.9 million and $24.8 million for the years ended December 31, 2001 and 2000, respectively. The increase of $13.1 million reflects the expansion and advancement of our pipeline. At December 31, 2001 we had 13 products in development compared to 11 at December 31, 2000. At the end of 2001 we had two products, LY900003 (ISIS 3521) and ISIS 2302, in Phase III clinical trials and six products in Phase II clinical trials compared to six in Phase II and III combined at the end of 2000. Expenditures related to LY900003 (ISIS 3521) in 2001 totaled $11.5 million, compared to $6.9 million in 2000. The increase of $4.6 million in 2001 over 2000 is a result of a full year of expenses for our Phase III trial of LY900003 (ISIS 3521) and the advancement of our Phase II trials for LY900003 (ISIS 3521). In January 2002, we completed the enrollment of our 600 patient Phase III trial for LY900003 (ISIS 3521) and we expect expenses to increase as we complete the trial and begin the activities required for the filing of the NDA.

Our second Phase III drug, ISIS 2302, had expenditures totaling $3.4 million in 2001 compared to $1.8 million in 2000. The increase of $1.6 million was primarily related to our efforts to evaluate the safety and efficacy of ISIS 2302 at doses higher than previously studied in our controlled trials, which were on-going in 1999. Expenditures for ISIS 2302 are expected to increase in 2002 as we incur expenses for the current Phase III trial initiated in 2001 and expenses for a second Phase III trial, which we plan to begin in 2002.

Ibis

Expenditures in our Ibis division have historically included costs for scientists, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of anti-infectives. With the award in October 2001 of a multi-year contract to fund up to $8.9 million from DARPA, Ibis expanded its program to include a diagnostic application of its technology. With the expansion of Ibis' program, we would expect to see expenses for the division increase. During 2001, under Ibis' existing agreements, it continued to incur expenses advancing its research efforts, as is evident by earning two milestone payments related to research advancements in its collaboration with Pfizer.

Ibis expenditures for the year ended December 31, 2001 totaled $6.5 million, compared to $5.2 million in 2000. The increase of $1.3 million was primarily a result of Ibis' continued drug discovery collaboration with Pfizer. Additionally, Ibis incurred expenses related to its performance obligations under its multi-year government contract with DARPA, awarded in the fourth quarter 2001.

R&D Support

Included in our research and development expenses are support costs such as rent, building and equipment repair and maintenance, utilities, depreciation of laboratory and manufacturing equipment, 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 22% to 25% of our total annual research and development expenses. R&D Support costs are directly related to our research and development efforts and typically fluctuate with research and development expenses. As our efforts increase in antisense drug discovery and development, and Ibis, we would expect to see an increase in R&D Support costs. However, R&D Support costs usually increase at a slower rate than our research and development expenses. In 2001 these costs were a smaller percentage of total research and development expenses than in 2000. Utilities costs did not significantly increase in 2001 over that incurred in recent years and we believe future utilities costs will not be material to our operations.

R&D Support costs for fiscal year 2001 totaled $18.4 million, compared to $14.5 million for 2000. The increase of $3.9 million is a direct result of increases in our research and development efforts. While we work to control R&D Support costs, they will increase as direct research and development costs increase. We expect R&D Support costs will increase in 2002 as we hire scientific personnel to support our Lilly collaboration, our government contracts, our GeneTrove collaborations and our expanding pipeline.

General and Administration

General and administration 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 accounting. Additionally, included in general and administration expenses are costs such as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that are required to support the corporate functions listed above.

General and administration expenses for the year totaled $11.1 million in 2001 compared to $8.6 million for the same period of 2000. This $2.5 million increase represents expenses required to support our increasing research and development activities. The number of transactions we completed with partners in 2001 resulted in increased expenses in most of our general and administrative functions, including business development, legal, human resources and accounting. As our research and development expenditures continue to increase we expect an increase in our general and administration expenditures. However, we expect general and administration expenses will increase at a slower rate then that of our research and development expenses.

Compensation Related to Stock Options

We reported $4.6 million and $587,000 as compensation related to stock options for the years ended December 31, 2001 and 2000, respectively. The expense was primarily a result of an option exchange program we offered to non-officer employees in January 2000. These exchanged options are required to be accounted for as variable stock options in accordance with Accounting Principles Board Opinion No. 25 and Financial Accounting Standard Board Interpretation No. 44. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. The increase of $4.0 million in 2001 over 2000 was primarily a result of the 109% increase in the price of our common stock as of December 31, 2001 compared to its price at December 31, 2000. In addition, we account for stock options granted to consultants in accordance with EITF 96-18, which also contributed to these expenses.

Our total operating expenses, which includes research and development, general and administration, compensation related to stock options, and restructuring activities were $99.4 million for the year ended December 31, 2001, compared to $67.9 million for the same period in 2000. The increase of $31.5 million came primarily from our research and development expenditures. Also contributing to the increase was expense recorded under compensation related to stock options and in our general and administrative expenditures. The increase was partially offset by the absence of restructuring activities present in 2000.

Equity in Loss of Affiliates

Equity in loss of affiliates for the year ended December 31, 2001 was $18.8 million compared to $16.2 million for the year ended December 31, 2000. As mentioned previously, we use the equity method of accounting for our investments in Orasense and HepaSense. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense under equity in loss of affiliates. As of December 31, 2001, our equity in loss of affiliates from Orasense and HepaSense totaled $10.3 million

and $8.3 million, respectively. In comparison, our equity in loss of affiliates as of December 31, 2000 was $9.7 million for Orasense, and $6.2 million for HepaSense. The increase in 2001 of $2.6 million is primarily a result of a full year of HepaSense activity reflected in 2001, while 2000 reflected eleven months of activity of which the first few months represented start-up efforts on our part. During 2000, we expanded our agreement with Pantheco A/S, or Pantheco, in which we obtained a 22% equity position. At the time that our investment increased above 20% we began using the equity method of accounting to record our investment in Pantheco's losses. We continued this accounting treatment until March 2001, when Pantheco issued additional shares of stock diluting our investment below 20%. At that time we discontinued accounting for the investment under the equity method and accounted for our investment as a long-term investment on our balance sheet.

Investment Income

Investment income remained relatively unchanged from 2000 to 2001. For the years ended December 31, 2001 and 2000, investment income was $6.4 million and $6.5 million, respectively. Although our average cash balance increased significantly in 2001, our investment income was directly affected by the decline in interest rates. The average return on investment grade bonds decreased in 2001 resulting in less interest income. In addition, in 2001 we realized a loss in an equity investment of approximately $515,000, which reduced our investment income for 2001.

Interest Expense

Interest expense increased to $15.2 million in 2001, compared with $13.2 million in 2000. The increase of $2.0 million in 2001 over 2000 is primarily related to debt arrangements where interest and principal payments are deferred. Interest and principal payments are deferred on our $40.1 million debt financing initiated in 1997 and 1998, and our borrowings under the Elan lines of credit for our Orasense and HepaSense joint ventures. As a result, interest expense increased in 2001 over that reported in 2000. Additionally, during 2001, we borrowed $5.6 million and $2.6 million from Elan under our Orasense and HepaSense lines of credit, respectively. Also contributing to the increase during 2001 were the effects of borrowing $20 million from our $100 million loan made available to us by Lilly. In 2001, $12.0 million of the $15.2 million in interest expense, which was accrued under various long-term debt agreements, did not require cash payments.

Net Loss Applicable to Common Stock

For the year ended December 31, 2001 and 2000, we reported a net loss of $73.8 million and $53.5 million, respectively. Our net loss applicable to common stock was $75.1 million for the year ended December 31, 2001, and $54.7 million in 2000, which includes $1.3 million and $1.2 million of accreted dividends on preferred stock as of December 31, 2001 and 2000, respectively. The increase of $20.3 million was primarily a result of increases in our operating expenses in 2001 from 2000. The increase was partially offset by increases in our total revenue.

Net Operating Loss Carryforward

At December 31, 2001, our net operating loss carryforward for federal income tax purposes was approximately $314.5 million. The net operating loss and research credit carryforwards make up the majority of our deferred tax assets. We will only be able to use the net operating loss and research credits, and realize the benefit of these deferred tax assets, if we become profitable. We have fully reserved all of our deferred tax assets, as their realization is uncertain. Our research credit carryforward for federal income tax purposes was approximately $21.1 million as of December 31, 2001. Our federal net operating loss and research credit

carryforwards will begin expiring in 2004 unless previously 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 or may not be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Years Ended December 31, 2000 and December 31, 1999

Total revenue for the year ended December 31, 2000 was $37.3 million, compared with $33.9 million in 1999. The increase of $3.4 million in revenue was primarily due to our sale of patents to Coley Pharmaceuticals Group and the licensing of our third generation antisense chemistry to Pantheco A/S. In addition, research and development revenues from affiliates increased due to our two joint ventures with Elan. The increase was offset by a decrease in research and development revenues under collaborative agreements.

Under the category research and development revenues under collaborative agreements, for the year ended December 31, 2000, we reported $16.9 million, compared to $29.4 million for 1999. The decrease of $12.5 million was principally due to the conclusion in December 1999 of development funding from Novartis and Boehringer Ingelheim. We delivered our first commercial shipment of Vitravene to our partner Novartis Ophthalmics in 1998. Since August 1998 we have earned $674,000 in revenue related to shipments of Vitravene to Novartis Ophthalmics.

Research and development revenue from affiliates was comprised of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. Orasense and HepaSense were formed in January 2000 and April 1999, respectively. During 2000, we recognized $5.2 million and $2.8 million from Orasense and HepaSense, respectively, as revenue. During 1999, we recognized $4.4 million from Orasense.

Our revenue from licensing and royalty activities was $12.4 million for the year ended December 31, 2000, compared with $166,000 in 1999. The increase in revenue of $12.2 million is primarily related to the sale of certain of our patents to Coley Pharmaceutical Group in 2000. Licensing and royalty revenue in 1999 was insignificant.

Research and development expenses decreased by 14% to $57.0 million in 2000, from $66.4 million in 1999. The $9.4 million decrease in 2000 over 1999 was primarily due to our restructuring and staff reductions that occurred early in 2000 offset by expenses related to the initiation in 2000 of a Phase III clinical trial for LY900003 (ISIS 3521) in non-small cell lung cancer.

Antisense drug discovery costs for the year ended December 31, 2000 totaled $12.5 million compared to $14.9 million for 1999. The decrease of $2.4 million was the result of restructuring and staff reductions that occurred at the beginning of 2000.

Ibis expenditures for the year ended December 31, 2000 totaled $5.2 million compared to $4.4 million in 1999. The increase of approximately $800,000 was primarily a result of continued research activities related to government grants and new activities related to our partnership with Pfizer.

Development expenditures totaled $24.8 million and $30.6 million for the years ended December 31, 2000 and 1999, respectively. The decrease of $5.8 million was the result of restructuring and staff reductions that occurred in 2000, as described above.

R&D Support expenditures totaled $14.5 million and $16.5 million for the years ended December 31, 2000 and 1999, respectively. The decrease of $2.0 million was the result of restructuring and staff reductions that occurred in 2000, as described above.

General and administrative expenses were $8.6 million for 2000, compared with $10.6 million in 1999. This decrease was primarily due to staff reductions related to our restructuring early in 2000.

Total operating expenses for 2000 were $67.9 million, compared with $77.0 million for 1999. Operating expenses for 2000 included $1.6 million in costs related to our restructuring and staff reductions that occurred early in 2000. Additionally, operating expenses included $0.6 million in non-cash compensation expense related to an option exchange program, which we offered to non-officer employees in January 2000, and the grant of stock options to consultants. We granted options to consultants at fair market value on the date of grant which are required to be accounted for in accordance with EITF 96-18.

Investment income increased to $6.5 million in 2000 from $2.5 million in 1999. This increase was principally due to our significantly higher average cash and short-term investment balances in 2000.

Interest expense increased to $13.2 million in 2000, compared with $11.4 million in 1999. The increase of $1.8 million in 2000 over 1999 was primarily related to debt arrangements where interest and principal payments are deferred. Interest and principal payments are deferred on our $40.1 million debt financing initiated in 1997 and 1998, and our borrowings under the Elan lines of credit for our Orasense and HepaSense joint ventures. As a result, interest expense increased in 2000 over that reported in 1999. Additionally, during 2000, we borrowed $6.7 million and $1.8 million from Elan under our Orasense and HepaSense lines of credit, respectively. The terms of the Elan debt provide that the payment of principal and interest is deferred until maturity in 2005 and 2006 for Orasense and HepaSense, respectively. In 2000, $9.7 million of the $13.2 million in interest expense, which was accrued under various long-term debt agreements, did not require cash payments.

Our net operating loss of $30.6 million in 2000 was 29% lower than our net operating loss of $43.1 million in 1999 for the reasons stated earlier. Our 2000 net loss applicable to common stock was $54.7 million, compared to $59.6 million in 1999. The 2000 loss applicable to common stock included $15.9 million for our equity in the losses of Orasense and HepaSense and $0.3 million for our equity in the loss of Pantheco. The 1999 net loss applicable to common stock included $7.2 million for our equity in the loss of Orasense.

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 revenues 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, 2001, we have earned approximately $270.3 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 $578.5 million from the sale of equity securities. We have borrowed approximately $113.3 million under long-term debt arrangements to finance a portion of our operations.

As of December 31, 2001, we had cash, cash equivalents and short-term investments of $312.0 million and working capital of $280.6 million. In comparison, we had cash, cash equivalents and short-term investments of $127.3 million and working capital of $118.6 million as of December 31, 2000. This increase in cash and short-term investments, and working capital, came primarily from our strategic alliance with Lilly, under which we received $130.8 million in 2001. From the Lilly alliance we received $75 million for the purchase of our common stock, $35.8 million related to the license of LY900003 (ISIS 3521) including development funding, and $20 million in draw downs on the interest-free $100 million loan to support the research collaboration. Also contributing to our cash position was our fourth quarter issuance of common stock in a secondary public offering in which we received $107.6 million, net of offering costs. In the second quarter of 2001, we received $22.5 million from the sale of our common stock to institutional investors. During 2001, we received proceeds of $7.2 million from employee stock option exercises and $11.4 million from proceeds related to our

long-term debt borrowings, excluding the $20 million loan draw down from Lilly. We received cash of $23.2 million from our collaborations with Merck, Pfizer, Amgen and Novartis, which added to our cash and short-term investments in 2001. For the year ended December 31, 2001, our net loss adjusted for non-cash items was $31.3 million, primarily to support the development of our 13 pipeline products. Additionally, we increased our working capital by $162.0 million, of which $97.4 million was related to an increase in our short-term investments in 2001 over 2000. Other significant cash uses in 2001 included $8.2 million related to our investments in our affiliates, $4.8 million in principal payments on debt and capital lease obligations, $15.0 million for the license associated with our Hybridon agreement and $9.3 million for purchases of property and equipment.

In 2001, Lilly made available to Isis a $100 million interest-free loan, to be used for the joint research collaboration. As of December 31, 2001, we had drawn down $20 million of the $100 million available. We are obligated to repay the $100 million loan at the end of the four-year research collaboration term. At our election, the loan can be repaid in either cash or our common stock at $40 per share.

Under the terms of our agreements with Elan, Elan will provide us with up to $18.4 million and $12.0 million in loans, which will be evidenced by convertible debt, to support our research and development activities related to Orasense and HepaSense, respectively. Restrictions on the availability of the debt facility are based on the anticipated collaboration costs and the balance of the funds available under each facility. As of December 31, 2001, we had drawn down $14.6 million under the Elan line of credit for Orasense, and our balance sheet reflected $16.7 million, which included accrued interest. Under a similar line of credit for HepaSense, we had drawn down $4.4 million as of December 31, 2001, and our balance sheet reflected $4.8 million. For a more detailed explanation of these lines of credit, see Note 3 to the Financial Statements, "Long-term Obligations and Commitments."

In 1997 and 1998, we borrowed a total of $40.1 million in private transactions. The loans must be repaid on November 1, 2007, and bear interest at 14% per annum. No payments of either principal or interest are required during the first five years of the loans. After the first five years, interest must be paid quarterly until the end of the loans. No principal payments are required until November 1, 2007. In conjunction with this transaction, we issued warrants to purchase 800,000 shares of common stock at a price of $25 per share. The warrants issued in connection with these financings expire on November 1, 2004. The warrants have been valued at a combined total of $5.4 million. This amount has been credited to stockholders' equity. Because interest is deferred during the first five years, the combined principal balance of both borrowings will accrue to a total of $78 million on November 1, 2002. The debt under these arrangements is carried on the balance sheet net of the unamortized amount allocated to the warrants and including accrued interest. The combined carrying amount of these notes at December 31, 2001 was $68.2 million. For a more detailed explanation of these lines of credit, see Note 3 to the Financial Statements, "Long-term Obligations and Commitments".

As of December 31, 2001, our long-term obligations, including the current portions, totaled $135.5 million, compared to $106.9 million at December 31, 2000. This increase was due primarily to the accrual of interest on the private debt financing together with the additional debt acquired during the year as described above. Additional capital lease financing to fund equipment acquisitions also contributed to the increase. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our business. We will continue to use lease lines as long as the terms continue to remain commercially attractive.

The following table summarizes our contractual obligations excluding interest as of December 31, 2001. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in 000s)				
	Total	Less than 1 year	1 - 3 years	4 - 5 years	After 5 years
Contractual Obligations					
Debt	$ 129,744	$ 7,310	$ 23,076	$ 31,142	$ 68,216
Capital Lease Obligations	$ 5,803	$ 2,527	$ 3,179	$ 97	$ —
Operating Leases	$ 11,014	$ 2,004	$ 3,693	$ 3,044	$ 2,273

We plan to continue to make significant expenditures to expand our research and development activities including our preclinical and clinical product development. We plan to continue to enter into more collaborations with partners which will provide for additional revenue to us and we may be required to incur additional expenses related to our obligations under many 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, such as 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.

We believe our cash, cash equivalents and short-term investments balances at December 31, 2001, combined with investment income and committed contractual cash payments, will be sufficient to meet our anticipated requirements for at least the next 36 months. However, because of the uncertainties in our business discussed in this section, and within our Risk Factors, this may not be the case. For a more detailed discussion of our risk factors, see the section titled "Risk Factors" beginning on page 28. In addition, we may choose to, or prevailing business conditions may require us to, obtain additional financing from time to time. We may choose to raise additional funds through public or private financing, licensing and contractual agreements or other arrangements. Additional funding, if needed, may not be available on terms favorable to us. Furthermore, any additional equity financing may be dilutive to our shareholders, and debt financing, if available, may involve restrictive covenants. If we choose to obtain funding through licensing and other contractual agreements, such agreements may require us to relinquish our rights to certain of our technologies or products. Our failure to raise capital when needed would harm our business, financial condition and results of operations.

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

Our financial statements and supplementary data required by this item are filed as exhibits hereto, are listed under Item 14(a)(1) and (2), and are incorporated herein by reference.

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

Not applicable.

PART III

ITEM 10. Directors and Executive Officers

The information required by this Item (with respect to Directors) is incorporated by reference from the information under the caption "Election of Directors" contained in our definitive Proxy Statement (the "Proxy Statement") which will be filed on or about April 5, 2002 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2002 Annual Meeting of stockholders to be held on May 31, 2002.

The required information concerning our Executive Officers is contained in Item 1, Part I of this Report. The information required by this Item concerning compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, is incorporated by reference from the information under the caption "Security Ownership of Certain Beneficial Owners and Management—Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy statement.

ITEM 11. Executive Compensation

"Compensation Committee Interlock and Insider Participation"

The information required by this item is incorporated by reference to the information under the caption "Executive Compensation" contained in the Proxy Statement.

ITEM 12. Security Ownership of Certain Beneficial Owners and Management

The information required by this item is incorporated by reference to the information under the caption "Security Ownership of Certain Beneficial Owners and Management" contained in the Proxy Statement.

ITEM 13. Certain Relationships and Related Transactions

The information required by this item is incorporated by reference to the information under the caption "Certain Transactions" contained in the Proxy Statement.

PART IV

ITEM 14. Exhibits, Financial Statement Schedules, and Reports on Form 8-K

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

See Index to Exhibits on pages 52 through 56.

(b) Reports on Form 8-K

On October 29, 2001, the Registrant filed a report on Form 8-K for a subcontract agreement between the registrant and Science Applications International Corporation, dated October 25, 2001, with a related press release.

On December 12, 2001, the Registrant filed a report on Form 8-K for a collaboration agreement between the registrant and OncoGenex Technologies Inc., dated November 16, 2001, with a related press release.

On January 4, 2002, the Registrant filed a report on Form 8-K which described several agreements the registrant entered into with Amgen, Inc., Integrated DNA Technolgoies, Inc., and Antisense Therapeutics Limited. In total seven documents were filed with related press releases. The following is a list of the agreements: a Collaboration Agreement dated December 11, 2001 with Amgen, Inc.; Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 and Amended and Restated IDT-Isis Agreement dated December 4, 2001 with Integrated DNA Technologies, Inc.; and a Master Agreement, Collaboration and License Agreement, Clinical Supply Agreement, and Stock Purchase Agreement, each dated October 31, 2001 with Antisense Therapeutics Limited.

On January 7, 2002, the Registrant filed a report on Form 8-K for a license agreement between the registrant and Eyetech Pharmaceuticals, Inc., dated December 31, 2001 and related press release dated January 7, 2002.

(c) Exhibits

The exhibits required by this Item are listed under Item 14(a)(3).

(d) Financial Statement Schedules

The financial statement schedules required by this Item are listed under Item 14(a)(2).

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 19th day of March, 2002.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE, M.D., PH.D.

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, M.D., PH.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	April 1, 2002

Stanley T. Crooke, M.D., Ph.D.		
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	April 1, 2002
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	April 1, 2002
/s/ WILLIAM R. MILLER William R. Miller	Director	April 1, 2002

/s/ FREDERICK T. MUTO Frederick T. Muto	Director	April 1, 2002
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	April 1, 2002
/s/ MARK B. SKALETSKY Mark B. Skaletsky	Director	April 1, 2002
/s/ JOHN C. REED John C. Reed	Director	April 1, 2002

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.(20)
3.3	—	Bylaws.(20)
4.1	—	Certificate of Designation of the Series A Convertible Preferred Stock.(11)
4.2	—	Certificate of Designation of the Series B Convertible Preferred Stock.(14)
4.3	—	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	—	Specimen Common Stock Certificate.(1)
4.5	—	Specimen Series A Preferred Stock Certificate.(18)
4.6	—	Specimen Series B Preferred Stock Certificate.(18)
4.7	—	Form of Right Certificate.(17)
4.8	—	Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(6)
4.9	—	First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(7)
4.10	—	Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(2)
4.11	—	Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense 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.(12)
4.12	—	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant, together with the related Amendment to the Stock Purchase Agreement.(13)
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.(21)
4.15	—	Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(21)
4.16	—	Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(21)
10.1	—	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)

10.2*	—	Registrant's 1989 Stock Option Plan, as amended.(6)
10.3*	—	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended.(4)

10.4*	—	Form of Performance-Based Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan entered into between the Registrant and certain of its officers together with related schedule.(24)
10.5*	—	Registrant's Employee Stock Purchase Plan.(10)
10.6*	—	Form of Employee Assignment of Patent Rights.(1)
10.7*	—	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan.(10)
10.8*	—	Severance Agreement dated January 11, 2000 entered into between the Registrant and its executive officers, together with related schedule.(10)
10.9	—	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(3)
10.10	—	Agreement between the Registrant and CIBA Vision Corporation (now Novartis Ophthalmics) dated July 10, 1997 (with certain confidentialinformation deleted).(5)
10.11	—	Amendment No. 2 to the Agreement between the Registrant and CIBA Vision Corporation, dated September 14, 1998(with certain confidential information deleted).(8)
10.12	—	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)
10.13	—	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)
10.14	—	Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(6)
10.15	—	First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(7)
10.16	—	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.17	—	Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted).(7)
10.18	—	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.19	—	Subscription, Joint Development and Operating Agreement, dated April 20, 1999 by and among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. And Orasense, 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 Agreements and License Agreements.(12)
10.20	—	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant; together with related Amendment to the Stock Purchase Agreement.(13)

10.21	—	Subscription, Joint Development and Operating Agreement, dated January 14, 2000 by and 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 Agreements and License Agreements.(14)
10.22	—	Agreement between the Registrant and Agouron Pharmaceuticals, dated June 9, 2000 (with certain confidential information deleted).(15)
10.23	—	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.24	—	Agreement between the Registrant and Merck & Co., Inc., dated May 22, 2001 (with certain confidential information deleted). (20)
10.25	—	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(20)
10.26	—	Agreement between the Registrant and PE Corporation through the Celera Genomics Group, dated July 9, 2001 (with certain confidential information deleted).(20)
10.27	—	Collaboration Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company. (with certain confidential information deleted).(21)
10.28	—	Development and License Agreement, dated August 14, 2001 between the Registrant and Eli Lilly and Company. (with certain confidential information deleted).(21)
10.29	—	LY900003 (ISIS 3521) Clinical Supply Agreement, dated August 29, 2001 between the Registrant and Eli Lilly and Company which is Exhibit B to the Development and License Agreement dated August 14, 2001 (i.e., Exhibit 10.2). (with certain confidential information deleted).(21)
10.30	—	Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(22)
10.31	—	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(25)
10.32	—	Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(25)
10.33	—	Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(25)
10.34	—	Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(25)
10.35	—	Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc.(23)
10.36	—	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(25)
10.37	—	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(25)

10.38	—	Collaboration Agreement dated December 11, 2001 between the Registrant and Amgen Inc.(25)
10.39	—	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc.(26)
10.40	—	Registrant's 10b5-1 Trading Plan.
10.41*	—	Registrant's 2002 Non-Employee Directors' Stock Option Plan.
10.42*	—	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.

21.1	—	List of Subsidiaries for the Registrant.
23.1	—	Consent of Ernst & Young LLP, Independent Auditors.
24.1	—	Power of Attorney. Reference is made to page 50.
99.1	—	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 the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.

(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1995 and incorporated herein by reference.

(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 Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.

(13) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 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. 333-90811) 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 an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.

(19) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71176) or amendments thereto and incorporated herein by reference.

(20) 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.

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

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

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

(24) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2000 and incorporated herein by reference.

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

(26) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 7, 2002 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 FINANCIAL STATEMENTS

REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors
Isis Pharmaceuticals, Inc.

We have audited the accompanying balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2001 and 2000, and the related statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2001. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

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

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Isis Pharmaceuticals, Inc. at December 31, 2001 and 2000, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2001, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

San Diego, California
February 1, 2002

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS

(in thousands, except share data)

	December 31, 2001	December 31, 2000
ASSETS		
Current assets:		
Cash and cash equivalents	$ 127,011	$ 39,615
Short-term investments	185,007	87,647
Contracts receivable	10,360	3,346
Other current assets	6,438	2,596
Total current assets	328,816	133,204
Property, plant and equipment, net	28,245	22,625
Licenses, net	32,361	500
Patent costs, net	16,735	13,815
Investments in affiliates	1,307	12,491
Deposits and other assets	5,298	621
Long-term investments	4,299	—
Total assets	$ 417,061	$ 183,256
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,126	$ 2,231

Accrued compensation	5,646	3,598
Accrued liabilities	3,942	1,429
Current portion of deferred contract revenues	22,696	2,771
Current portion of long-term obligations	9,837	4,607
Total current liabilities	48,247	14,636
Long-term obligations, less current portion	125,710	102,254
Long-term deferred revenue, less current portion	20,005	—
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value,120,150 shares authorized, issued and outstanding at December 31, 2001 and 2000	12,015	12,015
Accretion of Series A Preferred stock dividends	1,711	1,050
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 issued and outstanding at December 31, 2001 and 2000	12,015	12,015
Accretion of Series B Preferred stock dividends	1,222	584
Common stock, $.001 par value; 100,000,000 shares authorized, 53,750,318 shares and 40,086,447 shares issued and outstanding at December 31, 2001 and 2000, respectively	54	40
Additional paid-in capital	582,258	352,854
Deferred compensation	(245)	(858)
Accumulated other comprehensive income	660	126
Accumulated deficit	(386,591)	(311,460)
Total stockholders' equity	223,099	66,366
	$ 417,061	$ 183,256

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

	Years Ended December 31,		
	2001	2000	1999
Revenues:			
Research and development revenues under collaborative agreements	$ 40,396	$ 16,912	$ 29,357
Research and development revenues from affiliates	10,561	7,967	4,402
Licensing and royalty revenues	2,316	12,376	166
Total revenue	53,273	37,255	33,925
Expenses:			
Research and development (not including compensation related to stock options of $3,244 in 2001 and $435 in 2000)	83,741	57,014	66,413
General and administrative (not including compensation related to stock options of $1,329 in 2001 and $152 in 2000)	11,061	8,644	10,571
Compensation related to stock options	4,573	587	—
Restructuring activities	—	1,635	—
Total operating expenses	99,375	67,880	76,984
Loss from operations	(46,102)	(30,625)	(43,059)
Equity in loss of affiliates	(18,840)	(16,224)	(7,242)
Investment income	6,358	6,524	2,500
Interest expense	(15,248)	(13,160)	(11,424)
Net loss	(73,832)	(53,485)	(59,225)
Accretion of dividends on preferred stock	(1,299)	(1,214)	(420)
Net loss applicable to common stock	$ (75,131)	$ (54,699)	$ (59,645)
Basic and diluted net loss per share	$ (1.70)	$ (1.48)	$ (2.08)

Shares used in computing basic and diluted net loss per share	44,109	37,023	28,703

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY

Years Ended December 31, 2001, 2000 and 1999

(in thousands)

	Preferred stock			Common stock						
	Shares	Amount	Dividend Accretion	Shares	Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total Stockholders' Equity
Balance at December 31, 1998										
Comprehensive Loss	—	$ —	$ —	27,053	$ 27	$ 192,737	$ —	$ 166	$ (197,116)	$ (4,186)
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(59,645)	(59,645)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(195)	—	(195)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(59,840)
Issuance of preferred stock, Series A	120	12,015	—	—	—	—	—	—	—	12,015
Dividends accrued on preferred stock	—	—	420	—	—	—	—	—	—	420
Issuances of common stock, net of repurchases and offering costs	—	—	—	3,974	4	49,051	—	—	—	49,055
Warrants exercised	—	—	—	157	—	17	—	—	—	17
Options exercised and employee stock purchase plan	—	—	—	429	1	3,250	—	—	—	3,251
Compensation relating to the granting of options	—	—	—	—	—	137	—	—	—	137
Balance at December 31, 1999	120	12,015	420	31,613	32	245,192	—	(29)	(256,761)	869
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(54,699)	(54,699)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	155	—	155
Comprehensive loss	—	—	—	—	—	—	—	—	—	(54,544)
Issuance of preferred stock, Series B	12	12,015	—	—	—	—	—	—	—	12,015
Dividends accrued on preferred stock	—	—	1,214	—	—	—	—	—	—	1,214
Deferred compensation	—	—	—	—	—	1,445	(1,445)	—	—	—
Issuances of common stock,										
Net of offering costs	—	—	—	6,600	6	91,483	—	—	—	91,489
Options exercised andemployee stock purchase plan	—	—	—	1,873	2	14,734	—	—	—	14,736
Compensation relating to the granting of options	—	—	—	—	—	—	587	—	—	587
Balance at December 31, 2000	132	24,030	1,634	40,086	40	352,854	(858)	126	(311,460)	66,366
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(75,131)	(75,131)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	534	—	534
Comprehensive loss	—	—	—	—	—	—	—	—	—	(74,597)
Dividends accrued on preferred stock	—	—	1,299	—	—	—	—	—	—	1,299
Deferred compensation	—	—	—	—	—	3,960	(3,960)	—	—	—
Issuances of common stock, net	—	—	—	12,760	13	218,213	—	—	—	218,226

of offering costs										
Options exercised and employee stock purchase plan	—	—	—	904	1	7,231	—	—	—	7,232
Compensation relating to the granting of options	—	—	—	—	—	—	4,573	—	—	4,573
Balance at December 31, 2001	132	$ 24,030	$ 2,933	53,750	$ 54	$ 582,258	$ (245)	$ 660	$ (386,591)	$ 223,099

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS

(in thousands)

	Years Ended December 31,		
	2001	**2000**	**1999**
Operating activities:			
Net loss	$ (73,832)	(53,485)	$ (59,225)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	6,967	5,535	5,196
Compensation related to stock options	4,573	587	137
Deferred interest on long-term debt	12,017	9,685	8,077
Equity in losses of affiliates	18,840	16,224	7,242
Loss on investment	515	—	—
Equity in affiliate received in exchange for patent licensing	—	(1,125)	—
Write-off of patents	157	—	—
Write-off of inventory	—	301	—
Gain on disposal of property, plant and equipment	(570)	—	—
Changes in operating assets and liabilities:			
Contracts receivable	(7,014)	2,083	(1,963)
Other assets	(1,842)	(1,604)	220
Accounts payable	3,796	(917)	171
Accrued compensation	2,048	2,383	(1,873)
Accrued liabilities	2,943	(1,458)	(60)
Deferred contract revenues	25,244	(1,395)	(6,010)
Net cash used in operating activities	(6,158)	(23,186)	(48,088)
Investing activities:			
Purchase of short-term investments	(334,032)	(312,436)	(92,151)
Proceeds from the sale of short-term investments	236,236	242,487	105,643
Purchases of property, plant and equipment	(9,287)	(1,649)	(4,791)
Proceeds from the disposal of property, plant and equipment	500	—	—
Licenses and other assets	(28,674)	(3,182)	(2,642)
Investments in affiliates	(8,229)	(20,599)	(14,233)
Net cash used in investing activities	(143,486)	(95,379)	(8,174)
Financing activities:			
Net proceeds from issuance of equity	210,458	118,240	64,338
Proceeds from long-term borrowing	31,363	8,583	3,233
Principal payments on debt and capital lease obligations	(4,781)	(3,939)	(3,631)
Net cash provided by financing activities	237,040	122,884	63,940
Net increase in cash and cash equivalents	87,396	4,319	7,678
Cash and cash equivalents at beginning of year	39,615	35,296	27,618
Cash and cash equivalents at end of year	$ 127,011	$ 39,615	$ 35,296
Supplemental disclosures of cash flow information:			
Interest paid	$ 3,514	$ 3,454	$ 2,402
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt for patent acquisitions	$ 13,500	$ —	$ —

Additions to other current assets from sale of equipment	$	—	$	27	$	—
Repayment of debt with common stock	$	15,000	$	—	$	—
Addition to obligations for acquisition of property, plant, and equipment	$	1,184	$	—	$	—
Additions to long-term investment and deferred revenue for acquired corporate securities	$	2,759	$	—	$	—

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

December 31, 2001

1. Organization and Significant Accounting Policies

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 provisions of Statement of Financial Accounting Standards (SFAS) No. 128 *Earnings per Share*. Basic loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding during the period ("Basic EPS method"). Diluted earnings (loss) per common share is computed using the weighted-average number of common and dilutive common equivalent shares outstanding during the period ("Diluted EPS method"). Diluted common equivalent shares of 9.4 million at December 31, 2001 consist of shares issuable upon exercise of stock options, warrants, convertible debt and conversion of preferred stock. As Isis incurred a loss in the years ended December 31, 2001, 2000 and 1999, options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect would be antidilutive.

Contract revenues and expenses

Contract revenues consist of non-refundable research and development funding and are recorded as earned based on the performance requirements of the collaborative research and development contracts. Contract fees for which no further performance obligations exist are recognized when the payments are received or when the collection is assured. Payments received in excess of amounts earned are recorded as deferred contract revenues. Research and development costs are expensed as incurred. For the years ended December 31, 2001, 2000 and 1999, research and development costs and expenses of approximately $59.2 million, $28.4 million and $26.0 million, respectively, were related to collaborative research and development arrangements.

Revenue recognition

Revenue is generally recognized when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenues under collaborative agreements.

Research and development revenues under collaborative agreements are recognized as the related expenses are incurred, up to contractual limits. Payments received under these agreements that are related to future performance are deferred and recorded as revenue as they are earned over the specified future performance period. Revenue related to nonrefundable, upfront fees are recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue related to milestones are recognized upon completion of the milestone's performance requirement. Revenue from federal research grants are recorded during the period in which the related expenditures are incurred. Revenue from product sales, which have not been material, are recognized as the products are shipped.

Research and development revenues from affiliates

Research and development revenues from affiliates are recognized as the related expenses are incurred, up to contractual limits. Revenue related to milestones are recognized upon completion of the milestone's performance requirement.

Licensing and royalty revenues

Licensing and royalty revenues for which no services are required to be performed in the future are recognized immediately, if collectibility is reasonably assured.

Concentration of credit risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. The Company places its cash equivalents and short-term investments with high credit-quality financial institutions. The Company invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. The Company has established guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity. To date, the Company has not experienced significant losses on any of these investments.

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. The Company's short-term investments have initial maturities of greater than ninety days from date of purchase. The Company's securities are classified as "available-for-sale" in accordance with Statement of Financial Accounting Standards (SFAS) No. 115, *Accounting for Certain Investment in Debt and Equity Securities*. These investments are carried 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 year. The cost of debt securities sold is based on the specific identification method. Gross realized gains and losses are included in interest income and have not been material. See Note 2—Investments.

Property, plant and equipment

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

	December 31,	
	2001	2000
Land	$ 1,163	$ 1,163
Buildings and improvements	23,852	18,495
Equipment	36,078	32,750
Furniture and fixtures	1,604	1,521
	62,697	53,929
Less accumulated depreciation	(34,452)	(31,304)
	$ 28,245	$ 22,625

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
Leasehold improvements	10 years
Equipment	3-5 years
Furniture and fixtures	5 years

Patent costs

Isis capitalizes costs related to obtaining patents, consisting principally of legal and filing fees. These costs are regularly reviewed to determine that they include costs for patent applications Isis is pursuing. Costs related to patents that are not being actively pursued are evaluated under Accounting Principles Board Statement 17, *Accounting for Intangible Assets* and are adjusted to an appropriate amortization period or immediately written-off if appropriate. Patent costs are amortized 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 6.7 and 7.6 years at December 31, 2001 and 2000, respectively. Accumulated amortization related to patents was $2,282,000 and $1,615,000 at December 31, 2001 and 2000, respectively.

Investment in affiliates

Isis accounts for investments in joint ventures and other investments in 50% or less owned companies over which it has the ability to exercise significant influence using the equity method of accounting. At December 31, 2001 and 2000, the Company had the following investments accounted for using the equity method:

Orasense and HepaSense

In April 1999, Isis and Elan Corporation, plc (Elan) formed Orasense, Ltd., a Bermuda limited company. In January 2000, Isis and Elan Corporation, plc formed HepaSense, Ltd., a Bermuda limited company. Each joint venture is owned 80.1% by Isis and 19.9% by Elan. While Isis owns 80.1% of the outstanding common stock of Orasense and HepaSense, Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in Emerging Issues Task Force (EITF) No. 96-16. Accordingly, Isis accounts for its investment in each joint venture under the equity method of accounting.

Fair Value of Financial Instruments

The Company has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, short-term borrowings, accounts payable, current portion of notes payable and accrued expenses approximate the fair value because of their short maturities. Investment securities are reported at their estimated fair value based on quoted market prices of comparable instruments. The estimated fair value of fixed rate long-term debt is primarily based on the borrowing rates currently available to the Company for bank loans with similar terms and maturities. This fair value approximated the carrying amount of long-term debt at December 31, 2001.

Long-lived assets

In August 2001, the Financial Accounting Standards Board (FASB) issued SFAS No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets* (SFAS 144). This statement addresses financial accounting and reporting for the impairment or disposal of long-lived assets. SFAS 144 replaces SFAS No. 121, *Accounting for the Impairment of Long-Lived Assets and for Long-Lived Assets to be Disposed Of*, and amends the accounting and reporting provisions of Accounting Principles Board Opinion No. 30, *Reporting the Results of Operations—Reporting the Effects of Disposal of a Segment of a Business, and Extraordinary, Unusual, and Infrequently Occurring Events and Transactions*. The Company believes the adoption of this new standard will not have a material impact on the Company's financial statements.

Use of estimates

The preparation of 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 financial statements and accompanying notes. Actual results could differ from those estimates.

Stock Based Compensation

In March 2000, the FASB Interpretation Financial Interpretation (FIN) No. 44, *Accounting for Certain Transactions Involving Stock Compensation—an Interpretation of APB Opinion No. 25*. FIN 44 primarily clarifies (a) the definition of an employee for purposes of applying APB Opinion No. 25, (b) the criteria for determining whether a plan qualifies as a non-compensatory plan, (c) the accounting consequence of various modifications to the terms of previously fixed stock options or awards, and (d) the accounting for an exchange of stock compensation awards in a business combination. FIN 44 was effective July 1, 2000, but certain conclusions in FIN 44 cover specific events that occurred after either December 15, 1998 or January 12, 2000. 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, totaling 267,000 shares at December 31, 2001, are required to be accounted for as variable stock options in accordance with FIN 44 and the resulting compensation expense is reported 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.

Comprehensive income (loss)

SFAS No. 130, *Reporting Comprehensive Income* (SFAS 130) requires Isis to display comprehensive income (loss) and its components as part of Isis' full set of 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 were reported separately in stockholders' equity, to be included in accumulated other comprehensive income (loss). Comprehensive income (loss) for the years ended December 31, 2001, 2000 and 1999 have been reflected in the Statements of Stockholders' Equity.

Reclassification

Certain prior period amounts have been reclassified to conform to current presentation.

Impact of recently issued accounting standards

In July 2001, the FASB approved SFAS 142, *Goodwill and Other Intangible Assets*. SFAS 142 supercedes APB Opinion 17, *Intangible Assets*, and requires goodwill and other intangible assets acquired in a purchase transaction that have an indefinite useful life to no longer be amortized; however, these assets must be reviewed at least annually for impairment. Application of SFAS 142 is required beginning January 1, 2002. The adoption of SFAS 142 will not have a significant impact on the Company's financial statements.

2. Investments

Isis invests its excess cash in U.S. 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 take advantage of trends in yields and interest rates. Isis has not experienced any material losses on its short-term investments. As of December 31, 2001, 25% of the debt securities held by Isis had a contractual maturity of one year or less, and the remaining 75% of the portfolio was due within 3 years.

Through its research collaborations and license of its patents, Isis has acquired corporate securities of certain entities. These securities are generally restricted and therefore classified as non-current.

The following is a summary of Isis' investments, accounted for as available-for-sale securities:

	Available-for-Sale Securities		
	Cost	Unrealized Gains (Losses)	Estimated Fair Value
		(in thousands)	
December 31, 2001			
U.S. Treasury securities and obligations of U.S. Government agencies	$ 62,262	$ 204	$ 62,466
U.S. corporate debt securities	123,055	(514)	122,541
Corporate equity securities	3,329	970	4,299
Total	$ 188,646	$ 660	$ 189,306
Less current portion	$ 185,317	$ (310)	$ 185,007
Non current portion	$ 3,329	$ 970	$ 4,299

December 31, 2000			
U.S. Treasury securities and obligations of U.S. Government agencies	$ 26,161	$ (14)	$ 26,147
U.S. corporate debt securities	61,360	140	61,500
Total debt securities	$ 87,521	$ 126	$ 87,647

3. Long-Term Obligations and Commitments

In 1996 and 1997, Isis borrowed a total of $22,576,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim International GmbH. The borrowed funds were used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and range from 8.36% to 8.46%. Interest

payments are due twice each year with principal repayment due seven years after the advance date. The principal may be repaid in cash or stock, at Isis' option. If Isis elects to repay the loan in shares of Isis common stock, repayment will be made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of December 31, 2001 and 2000 was $22,576,000, which approximated fair value.

In 1997, Isis obtained two term loans from a bank to refinance existing notes secured by real property and to fund facilities expansion. Both notes are secured by Isis' real property and bear interest at the prime interest rate (4.75% and 9.5% at December 31, 2001 and 2000, respectively) plus 0.5%. The first note in the amount of $3,707,000 requires monthly principal repayments of $12,433 plus interest with the remaining principal balance due in July 2002. The balance of this first note at December 31, 2001 and 2000 was $2,991,000 and $3,140,000, respectively. The second note in the amount of $6,000,000 requires monthly principal repayments of $50,000 plus related interest with the remaining principal balance due in July 2002. The balance at December 31, 2001 and 2000 was $3,300,000 and $3,900,000, respectively. As of December 31, 2001 and 2000, the carrying value of these variable rate long-term notes approximated fair value.

Between 1997 and 1998, Isis obtained a total of $40,060,000 in private debt financing. The terms of the financing provide for a ten-year maturity on the debt, interest of 14% per annum and deferred interest payments for the first five years of the loan. After the first five years, interest must be paid quarterly until the end of the loan, which is November 1, 2007. No principal repayments are required until the end of the loan. Because interest is deferred during the first five years, the principal balance will be $78 million on November 1, 2002. In conjunction with the debt financing, Isis issued to the lender warrants to purchase a total of 800,000 shares of Isis' common stock. The warrants are exercisable at $25 per share. The fair value of the warrants of $5,426,000 was estimated using the Black-Scholes option pricing model, with the following assumptions: expected life of 4.5 years, expected dividend yield of zero percent, expected volatility of 60 percent and a risk free interest rate of 5.9%. The allocation of value to the warrants creates a debt discount, which is amortized using the effective interest method. The effective interest rate of this debt is approximately 16%. The debt of $68,216,000 and $57,995,000 at December 31, 2001 and 2000, respectively, is carried on the balance sheet net of the unamortized debt discount and includes accrued interest. The fair value of this debt at December 31, 2001 and 2000 approximated $68,216,000 and $60,479,000, respectively.

In December 1998, Isis purchased from Gilead Sciences, Inc., the holdings of Gilead's antisense patent estate. This acquisition included patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over three years. Isis recorded the net present value of the future payments, using a discount rate of 10%. In accordance with the agreement, Isis made its final payment to Gilead in December 2001, therefore there was no outstanding balance at December 31, 2001.

In April 1999, Elan International Services made available to Isis an $18,400,000 line of credit under a convertible debt arrangement made in conjunction with the Orasense joint venture. The terms of the convertible debt provide interest at 12% per annum, compounded semi-annually, maturing April 19, 2005. No principal or interest payments are required until the end of the loan. The loan may be prepaid by Isis at any time, at its option, in whole or in part, in cash or in common stock (at a price equal to the average market value of the common stock for the 60 trading days ending two business days prior to the date of prepayment). At any time prior to maturity, EIS may convert all or any portion of the loan outstanding, on a per tranche basis, into the number of shares of common stock obtained by dividing the amount to be converted by 150% of the average market value of the common

stock for the 60 trading days ending two business days prior to the date of disbursement of such tranche. This debt facility is subordinate to the $40,000,000 private debt financing which matures November 2007. During 2001 and 2000, Isis borrowed $5,601,000 and $6,749,000, respectively, under this convertible debt agreement to provide development funding to Orasense. Based on the principal and accrued interest outstanding at December 31, 2001, the loan balance due at maturity will be $23,122,000, provided that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility, including accrued interest, as of December 31, 2001 and 2000 was $16,706,000 and $9,724,000, respectively, which approximated fair value.

In September 1999, Isis borrowed $1,019,000 from Abbott Laboratories, Inc. to be used by Isis as its contribution toward costs associated with Abbott's design and construction of a facility for commercial scale manufacturing of oligonucleotides. The terms of the financing provide for the debt to be paid off in December 2002, with an annual interest rate of 2% over the Citibank prime rate calculated annually at the date of borrowing. The interest rate on this debt was 8.5% and 11.5% at December 31, 2001 and 2000, respectively. Interest is payable annually. The principal, which is due at maturity, can be paid in cash, common stock (based on 100% of the average closing price for the 20 trading days preceding loan maturity), or through increasing the price Isis would pay for the oligonucleotides produced by Abbott until the loan is repaid. The balance under this borrowing facility as of December 31, 2001 and 2000 was $1,019,000, which approximated fair value.

In January 2000, EIS made available to Isis a $12,000,000 line of credit under a convertible debt arrangement made in conjunction with the HepaSense joint venture. The terms of the convertible debt provide interest at 12% per annum, compounded semi-annually, maturing January 14, 2006. No principal or interest payments are required until the end of the loan. The loan may be prepaid by Isis at any time, at its option, in whole or in part, in cash or in common stock (at a price equal to 95% of the average market value of the common stock for the 60 trading days ending two business days prior to the date of repayment); provided that no more than 50% of any prepayment amount shall be payable by the Company in the Company's common stock. At any time prior to maturity, EIS may

convert all or any portion of the loan outstanding, on a per tranche basis, into the number of shares of common stock obtained by dividing the amount to be converted by 140% of the average market value of the common stock for the 60 trading days ending two business days prior to the date of disbursement of such tranche. This debt facility is subordinate to the $40,000,000 private debt financing which matures November 2007. During 2001 and 2000, Isis borrowed $2,596,000 and $1,834,000, respectively, under this convertible debt agreement to provide development funding to HepaSense. Based on the principal and accrued interest outstanding at December 31, 2001, the loan balance due at maturity will be $7,042,000, providing that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility, included accrued interest, as of December 31, 2001 and 2000 was $4,771,000 and $1,856,000, respectively, which approximated fair value.

In August 2001, Eli Lilly and Company made available to Isis a $100 million loan, to be used for the joint research collaboration between the two companies. The loan is interest-free and is repayable, at Isis' 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 Isis. As of December 31, 2001, the Company had drawn down $20 million of the $100 million available. The Company is accounting for the line of credit at an imputed interest rate of 20% consistent with market conditions in place at the time the loan was agreed to. The Company will carry the net present value of its draw downs as a long-term obligation and record interest expense over the term of the loan. Additionally, the related deferred interest is accounted for as long-term deferred revenue and will be amortized into revenue over the term of the

loan. At December 31, 2001, the balance in long-term obligations was $9,665,000 and the balance in deferred revenue was $10,335,000.

Annual debt maturities at December 31, 2001 are as follows (in thousands):

2002	$ 7,310
2003	16,700
2004	6,376
2005	26,371
2006	4,771
Thereafter	68,216
Total	$ 129,744

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through July 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, 2001 are as follows (in thousands):

	Operating Leases	Capital Leases
2002	$ 2,004	$ 2,944
2003	1,959	2,286
2004	1,734	1,172
2005	1,506	141
2006	1,538	—
Thereafter	2,273	—
Total minimum payments	$ 11,014	$ 6,543
Less amount representing interest		(740)
Present value of future minimum payments		5,803
Less current portion		(2,527)
Long-term portion		$ 3,276

Rent expense for the years ended December 31, 2001, 2000, and 1999 was $2,264,000, $2,115,000, and $1,736,000, respectively. Cost of equipment under capital leases at December 31, 2001 and 2000 was $12,959,000 and $9,754,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2001 and 2000 was approximately $7,600,000 and $5,425,000, respectively.

4. Stockholders' Equity

Preferred Stock

The Company is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. Outstanding preferred stock consists of Series A and Series B Convertible Exchangeable 5% Preferred Stock. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series A Convertible Exchangeable 5% Preferred Stock

At December 31, 2001, Isis had 120,150 shares authorized, issued and outstanding of Series A Convertible Exchangeable 5% Preferred Stock. The shares have a term of six years and are convertible into Isis' common stock on or after March 31, 2002 at 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to March 31, 2002, or automatically in the event of a significant transaction, at 120% of the average closing price

of Isis common stock for the 60 trading days ending two business days prior to the transaction if the significant transaction occurs prior to March 31, 2002, or 125% if the significant transaction occurs thereafter. The Preferred Stock is exchangeable at the option of Elan at any time through and including June 30, 2002 for an incremental 30.1% of the issued and outstanding shares owned by Isis of Orasense. It also bears a mandatory pay-in-kind dividend of 5.0% per year based on the original issue price per share, compounded semi-annually payable only upon conversion into Isis' common stock or cash.

Series B Convertible Exchangeable 5% Preferred Stock

At December 31, 2001, Isis had 16,620 shares authorized, of which 12,015 shares were issued and outstanding, of Series B Convertible Exchangeable 5% Preferred Stock. The shares have a term of six years and are convertible into Isis' common stock on or after June 30, 2002 at 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to June 30, 2002, or automatically in the event of a significant transaction, at 120% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to the transaction if the significant event occurs prior to June 30, 2002, or 125% if the significant transaction occurs on or after June 30, 2002. The Preferred Stock is also exchangeable for the ownership Isis holds in HepaSense. It also bears a mandatory pay-in-kind dividend of 5.0% per year based on the original issue price per share, compounded semi-annually payable only upon conversion into Isis' common stock or cash.

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. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20 percent 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, the Rights may be redeemed by the Company's Board of Directors in whole, but not in part, at a price of $0.001 per Right.

Common Stock

During 2001, Isis issued 1,986,874 shares of common stock to institutional investors at prices ranging from $11.03 to $11.50 per share. In October 2001, Isis filed a registration statement on Form S-3, including an amendment, with the Securities and Exchange Commission for the sole purpose

of registering the resale of 857,143 shares of Isis common stock, which Isis issued to Hybridon in September 2001 in accordance with Isis' agreement with Hybridon entered into in May 2001.

In August 2001, the Company issued 4,166,667 shares of its common stock to Lilly at $18.00 per share in conjunction with the signing of the Research Collaboration and Development and License Agreements. The Company incurred $1,850,000 in offering costs which were netted against proceeds in stockholder's equity.

In October 2001, Isis issued 5,750,000 shares of its common stock in a secondary public offering at $20.00 per share. The Company recorded proceeds from the offering of approximately $107.6 million net of offering costs, which included underwriter's fees of $6.9 million.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis adopted a stock option plan which provides for the issuance of non-qualified and incentive stock options for the purchase of up to 10,200,000 shares of common stock to its employees and certain other individuals. The plan also includes provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. Typically, options expire 10 years from the date of grant. 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 vest over a five-year period. At December 31, 2001, a total of 5,886,000 options were outstanding, options to purchase 3,589,000 shares were exercisable, and 61,000 shares were available for future grant. In fiscal year 1991 Isis granted 412,000 non-qualified stock options for common stock to certain individuals. At December 31, 2001, there were no non-qualified options outstanding and no shares were available for future grant.

1992 Non-Employee Directors' Stock Option Plan

In July 1992, Isis adopted the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options for the purchase of up to 300,000 shares of common stock to Isis's non-employee directors. Options under this plan expire 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in four equal annual installments beginning one year after the date of grant. Options granted before January 1, 1996 vest over a five-year period. At December 31, 2001, a total of 183,000 options were outstanding, 121,000 shares issued under this plan were exercisable and 48,000 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. 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. Under the 2000 Plan, a total of 2,151,000 options were outstanding, 622,000 shares were exercisable, and 1,658,000 shares were available for future grant at December 31, 2001.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis adopted an amendment and restatement of its 1992 Non-Employee Directors' Stock Option Plan. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has 600,000 shares of common stock reserved for issuance.

The following table summarizes stock option activity for the years ended December 31, 1999 through December 31, 2001 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Avg Price Per Share
Outstanding at December 31, 1998	6,986	$0.14 to $19.88	$ 10.27
Granted	1,539	$4.00 to $18.00	
Exercised	(333)	$0.14 to $14.50	
Terminated	(490)	$3.88 to $19.75	
Outstanding at December 31, 1999	7,702	$0.43 to $19.88	$ 10.68
Granted	4,069	$6.25 to $17.69	
Exercised	(1,800)	$0.42 to $19.38	
Terminated	(2,300)	$5.75 to $19.88	
Outstanding at December 31, 2000	7,671	$3.57 to $18.63	$ 9.21
Granted	1,893	$8.38 to $26.65	
Exercised	(817)	$3.57 to $18.00	
Terminated	(527)	$6.19 to $21.50	
Outstanding at December 31, 2001	8,220	$3.75 to $26.65	$ 9.88

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 12/31/01	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/01	Weighted Average Exercise Price
$ 3.75 - $5.88	490	2.59	$ 4.52	490	$ 4.52
$ 6.00 - $6.88	2,697	6.17	$ 6.73	1,392	$ 6.67
$ 7.00 - $8.88	324	4.87	$ 8.00	203	$ 7.67
$ 9.00 - $9.94	1,183	7.59	$ 9.59	270	$ 9.57
$ 10.00 - $10.94	627	8.01	$ 10.34	250	$ 10.31
$ 11.00 - $11.99	307	8.31	$ 11.49	87	$ 11.45
$ 12.00 - $12.94	1,505	6.85	$ 12.51	1,001	$ 12.55
$ 13.00 - $14.98	456	5.47	$ 13.54	374	$ 13.40
$ 15.00 - $17.88	223	7.25	$ 16.29	113	$ 16.16
$ 18.00 - $19.89	198	6.14	$ 18.19	152	$ 18.07
$ 20.00 - $26.65	210	9.86	$ 22.00	—	$ —
$ 3.75 - $26.65	8,220	6.53	$ 9.88	4,332	$ 9.55

Employee Stock Purchase Plan

In 1991, the Board of Directors adopted and the stockholders subsequently approved, the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance thereunder.

In 2000, the common stock under the Employee Stock Purchase Plan was fully issued; as a result a second plan was instituted. During 2001, an additional 200,000 shares of common stock were reserved for the 2000 Employee Stock Purchase 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 2001, 87,000 shares were issued under this plan to employees at prices ranging from $8.18 to $9.03 per share. At December 31, 2001, 285,000 shares were available for purchase under this plan.

Stock-Based Employee Compensation

Isis has adopted the disclosure-only provision of Statement of Financial Accounting Standards No. 123, *Accounting for Stock-Based Compensation*. Accordingly, no compensation expense has been recognized for the stock option plans. Had compensation expense been determined consistent with Statement No. 123, Isis' net loss and basic net loss per share would have been changed to the following pro forma amounts (in thousands, except per share amounts):

	2001	2000	1999
Net loss—as reported	$ (75,131)	$ (54,699)	$ (59,645)

Net loss—pro forma	$ (82,598)	$ (63,110)	$ (69,446)
Basic net loss per share—as reported	$ (1.70)	$ (1.48)	$ (2.08)
Basic net loss per share—pro forma	$ (1.87)	$ (1.71)	$ (2.42)

The fair value of each option grant is estimated on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions for 2001: a risk-free interest rate of 4.5%; a dividend yield of 0%; a volatility factor of 79.1% and an option life of 5.7 years; for 2000: a risk-free interest rate of 6%; a dividend yield of 0%; a volatility factor of 80.0% and an option life of 4.2 years; and for 1999: a risk-free interest rate of 5.7%; a dividend yield of 0%; a volatility factor of 60.0% and an option life of 3.7 years. The weighted average fair value of options granted was $12.14 for 2001, $7.81 for 2000, and $6.41 for 1999.

Warrants

In 1997 and 1998, Isis issued 500,000 and 300,000 warrants, respectively, in conjunction with a private debt financing agreement. As of December 31, 2001, all of the warrants remain outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3.

In 1999, Isis issued 215,000 warrants to Elan International Services, Ltd. as part of the joint venture collaboration between Isis and Elan to form Orasense. As of December 31, 2001, all of the warrants remained outstanding at an exercise price of $24 per share. The warrants expire April 19, 2004.

In 2000, Isis issued 14,881 warrants to Elan International Services, Ltd. as part of the joint venture collaboration between Isis and Elan to form HepaSense. As of December 31, 2001, all of the warrants remained outstanding at an exercise price of $50.40 per share. The warrants expire May 1, 2008.

As of December 31, 2001, total common shares reserved for future issuance was approximately 11,935,000.

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2001 and 2000 are shown below. Valuation allowances of $169,032,000 and $133,535,000 have been recognized for 2001 and 2000, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2001	2000
Deferred tax assets:		
Capitalized research expense	$ 6,685,000	$ 10,856,000
Net operating loss carryforwards	111,514,000	104,766,000
Research and development credits	29,572,000	17,351,000
Deferred revenue	18,047,000	1,190,000
Other, net	4,305,000	4,959,000
Total deferred tax assets	170,123,000	139,122,000
Deferred tax liabilities:		
Patent expense	(1,091,000)	(5,587,000)
Total deferred tax liabilities	(1,091,000)	(5,587,000)
Total net deferred tax assets	169,032,000	133,535,000
Valuation allowance for deferred tax assets	(169,032,000)	(133,535,000)
Net deferred tax assets	$ —	$ —

At December 31, 2001, approximately $16,273,000 of the valuation allowance for deferred tax assets relates to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2001, Isis had federal and California tax net operating loss carryforwards of approximately $314,485,000 and $25,726,000, respectively. Isis also had federal and California research credit carryforwards of approximately $21,051,000 and $12,184,000, 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 55% limitation in the utilization of California loss carryforwards. The federal tax loss carryforward and the research credit carryforwards will begin expiring in 2004 unless previously utilized. Approximately $354,000 of the California tax loss carryforward expired during 2001 and the related deferred tax asset and tax loss carryforward amounts have been reduced accordingly. The remaining California tax loss carryforward will continue expiring in 2002, unless utilized.

Annual use of Isis' net operating loss and credit carryforwards will be limited under the Internal Revenue Code as a result of cumulative changes in ownership of more than 50% during the periods ended December 31, 1989 and 1991. However, Isis believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. Research and Development Collaborative Arrangements and Licensing Agreements

In 1990, Isis entered into a collaborative agreement with Novartis to discover and investigate oligonucleotide compounds active against specific targets, which was expanded in 1996 to include the development of LY900003 (ISIS 3521) and ISIS 5132. During 1999, Novartis concluded its participation in the development of LY900003 (ISIS 3521) and ISIS 5132, and as a result no further revenue was recognized in 2001 and 2000. Included in the statement of operations as research and development revenues under collaborative agreements for the year ended December 31, 1999 are revenues totaling $7,527,000.

In July 1995, Isis and Boehringer Ingelheim International GmbH signed definitive agreements and formed a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2 million shares of Isis's common stock for $28.5 million in cash plus certain license rights. Boehringer Ingelheim and Isis provided equal funding for the combined research and development program, which came to a conclusion in December 1999. As a result, there was no related revenue included in the statement of operations for 2001 and 2000. For the year ended December 31, 1999, Isis recognized research and development revenues under collaborative agreements of $6,974,000.

In July 1997, Isis and Novartis Ophthalmics, formerly CIBA Vision Corporation, entered into an agreement granting Novartis Ophthalmics exclusive worldwide distribution rights for Vitravene™ (fomivirsen). Under the terms of the agreement, Isis will manufacture and sell Vitravene to Novartis Ophthalmics, who is responsible for worldwide sales and marketing. In August 1998, the FDA approved Vitravene for marketing. Since 1998, Isis has recognized $674,000 in revenue related to shipments of Vitravene, which is included in the statement of operations under research and development revenues under collaborative agreements. Under the Novartis Ophthalmics agreement, Isis earned a $2.5 million milestone payment in each of 2001, 2000 and 1999, which were included in the statement of operations as research and development revenues under collaborative agreements.

In June 1998, Isis entered into a research collaboration with Merck & Co., Inc. to discover small molecule drug candidates to treat patients infected with Hepatitis C virus, or HCV. Isis and Merck will design, synthesize, and evaluate novel compounds that Merck will screen in its proprietary assays for identifying HCV replication inhibitors. Merck has the right to commercialize drugs arising from the collaboration, and Isis retains the right to use technology developed in the collaboration in its antisense program. In March 2001, Isis and Merck extended this research collaboration for an additional year. The collaboration provides Isis with annual research support and milestone payments and royalties upon commercialization. Included in the statement of operations as research and development revenues under collaborative agreements for the years ended December 31, 2001, 2000 and 1999, are revenues of $3,590,000, $3,000,000 and $3,500,000, respectively, from Merck under the terms of this agreement. The 2001 revenue of $3,590,000 included a $1.5 million milestone payment that Isis earned in 2001.

As part of a licensing agreement for Isis' novel antisense chemistry Peptide Nucleic Acid (PNA), completed in November 1998, Isis received common shares in Pantheco A/S. At that time, a value for the equity position was not determinable and no carrying value was given to the common shares. In September 2000, Isis entered into a second license for PNA with Pantheco, where Isis received additional common shares upon the completion of Pantheco's October 2000 financing. Isis has no obligations under the agreements. As a result of Pantheco's October 2000 financing, Isis' total ownership in Pantheco was 22% and valued at approximately $1.1 million. In March 2001 Pantheco issued additional shares which diluted Isis' holdings in Pantheco to 18%. For the year ended December 31, 2000 Isis recorded $1.1 million as licensing revenue. For the years ended December 31, 2001 and 2000, Isis recorded $267,000 and $285,000, respectively, under equity in loss of affiliates.

In December 1998, Isis entered into a collaborative research agreement with AstraZeneca Pharmaceuticals to discover, develop and commercialize novel antisense-based cancer drugs. The initial term of the research collaboration was three years with a clause that allowed AstraZeneca to terminate at the end of the second year. In December 2000, AstraZeneca terminated the agreement. As a result, there was no related revenue included in the statement of operations for 2001. Included in the statement of operations as research and development revenues under collaborative agreements for the years ended December 31, 2000 and 1999 are revenues of $3,420,000 from AstraZeneca under the terms of this agreement.

In April 1999, Isis and Elan formed a joint venture, Orasense, to develop technology for the formulation of oral oligonucleotide drugs. The joint venture is currently owned 80.1% by Isis and

19.9% by Elan. Isis and Elan each contributed rights to certain oral drug delivery technology to the joint venture. In addition, Isis contributed rights to a proprietary oligonucleotide, which will be the first candidate for oral formulation by Orasense. Isis and Elan will provide development and manufacturing services to Orasense and will be entitled to royalties on any milestone payments and royalties received by Orasense for development of orally formulated oligonucleotide drugs. If Isis enters into an agreement with Orasense for oral formulation of any Isis oligonucleotide drug, Isis will pay Orasense royalties and a portion of certain third party milestone payments with respect to the drug. In conjunction with this transaction, Isis sold 910,844 shares of Isis' common stock to Elan International Services, or EIS, for $15 million, and issued a warrant to purchase up to 215,000 shares of Isis' common stock at $24 per share. The term of the warrant is five years. Isis also sold 120,150 shares of Isis' Series A Convertible Preferred Stock to EIS for $12,015,000 (See Note 4). For the years ended December 31, 2001, 2000 and 1999, Isis recorded $5,359,000, $5,217,000 and $4,402,000, respectively, in revenue from Orasense. For the years ended December 31, 2001, 2000 and 1999, Isis recorded $10,297,000, $9,702,000 and 7,242,000, respectively, as equity in the net loss of Orasense. Additionally, at December 31, 2001 and 2000, the balance sheet included $1,706,000 and $968,000, respectively, of contracts receivable relating to Orasense.

In September 1999, Isis entered into a three-year target validation collaboration with Aventis (formerly Rhone-Poulenc Rorer). The collaboration uses Isis' target validation technology to assess genes identified within Aventis' genomics programs. This collaboration enables Aventis to determine the function and therapeutic value of numerous novel gene targets and to use this information about gene function to develop pharmaceutical products. It also provides Isis with valuable information on these targets to assist in the development of novel antisense drugs. Under the terms of the agreement, Aventis will pay Isis research fees and milestone payments based on the success of the program. For the years ended December 31, 2001, 2000 and 1999, Isis recorded revenue of $598,000, $1,062,000 and $200,000, respectively, in the statement of operations as research and development revenues from collaborative agreements.

In January 2000, Isis and Elan formed a new joint venture, HepaSense, to develop an antisense drug to treat patients chronically infected with HCV. This new joint venture is currently owned 80.1% by Isis and 19.9% by Elan. HepaSense plans to develop and commercialize this novel therapeutic for HCV, while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD® Drug Delivery System, a disposable subcutaneous infusion device. Isis and Elan have each licensed technology to HepaSense. Isis and Elan will provide development and manufacturing services to HepaSense and will be entitled to royalties on proceeds received by HepaSense for development of HCV drugs. In conjunction with this transaction, Isis sold 297,619 shares of Isis' common stock to EIS for $7,500,000, and issued a warrant to purchase up to 14,881 shares of Isis' common stock at $50.40 per share. The term of the warrant is five years. Isis also sold 12,015 shares of Isis' Series B Convertible Preferred Stock to EIS for $12,015,000 (See Note 4). For the years ended December 31, 2001 and 2000, Isis recorded $5,202,000 and $2,751,000, respectively, in revenue from HepaSense. For the years ended December 31, 2001 and 2000, Isis recorded $8,276,000 and $6,237,000, respectively, as equity in the net loss of HepaSense. Additionally, at December 31, 2001 and 2000, the balance sheet included $2,498,000 and $481,000, respectively, of contracts receivable relating to HepaSense.

In June 2000, Ibis and Pfizer entered into a collaboration for the discovery and development of small molecule drugs against certain RNA targets. Using Ibis' proprietary technology and Pfizer's expertise in small molecule drug discovery, the collaboration focuses on discovering drugs that bind to RNA. Pfizer agreed to fund collaborative research, pay an up-front technology access fee and make milestone payments. In addition, under the terms of the agreement, Pfizer agreed to develop and commercialize drugs discovered through the collaboration. Also, Pfizer agreed to pay Isis royalties on sales of any drugs resulting from the collaboration. In May 2001 and October 2001, Ibis earned a $2.5 million milestone payment and a $1.5 million milestone payment, respectively, for progress in this

collaboration. This collaboration is scheduled to end in June 2002. For the years ended December 31, 2001 and 2000, Isis recorded $7,325,000 and $2,393,000 in total revenues, which were included in the statement of operations as research and development revenues under collaborative agreements. The 2001 revenue of $7,325,000 includes the $4.0 million in milestone payments that Ibis earned in 2001.

In July 2000, Isis entered into a target validation agreement with R.W. Johnson Pharmaceutical Research Institute, a division of Ortho-McNeil Pharmaceutical, Inc. This agreement was subsequently assigned to Johnson & Johnson Pharmaceutical Research & Development, LLC, or J&JPRD. Under the agreement, Isis is using its proprietary target validation technology to assess and prioritize genes identified by J&JPRD. This collaboration may enable J&JPRD to determine the function and therapeutic value of novel gene targets. It also provides Isis with information on these targets to assist in its development of novel antisense drugs. The initial term of this collaboration is for one year after the shipment of the last antisense inhibitor. Isis recorded revenues associated with this agreement in the statement of operations as research and development revenues under collaborative agreements.

In September 2000, Isis sold its patents concerning the use of phosphorothioate oligonucleotides for activating the immune system to Coley Pharmaceutical Group. The patents were originally licensed to Coley in 1998 for a limited scope of use, at which time Coley paid Isis $5 million in cash and issued preferred stock to Isis. In exchange for all nonantisense rights to this group of immunomodulation patents and in lieu of any and all future payments that could potentially be owed under the original agreement, Coley paid Isis an additional $10.7 million in 2000. For the year ended December 31, 2000, Isis recognized $10.7 million in revenue, which was included in the statement of operations as licensing and royalty revenues.

In December 2000, Isis' GeneTrove division, extended its target validation collaboration with Abbott Laboratories, Inc., which began in December 1998, for an additional two years. Through the collaboration, Isis utilizes its target validation technology to enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Under the original agreement, Abbott agreed to pay Isis an up-front fee, research fees, milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. Isis also received rights to develop drugs for Abbott targeting Abbott proprietary genes. Included in the statement of operations as research and development revenues under collaborative agreements for the years ended December 31, 2001, 2000 and 1999 are revenues of $668,000, $1,000,000, and $1,250,000, respectively, from Abbott under the terms of this agreement.

In March 2001, Isis and Molecular Biosystems, Inc. amended a non-exclusive Patent License Agreement originally entered into in September 1992. The amendment provided Isis with a fully paid up license to certain patents and patent applications in exchange for a one-time payment of $1 million. Isis recorded the payment as licensed technology and is amortizing the amount over the estimated useful life of the patents.

In May 2001, Isis agreed to license to Merck its preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. Merck has the right to undertake the future development and commercialization of the compound. Isis received an upfront payment for certain expenses associated with the preclinical development of the drug. In addition, Merck agreed to pay Isis research fees, a series of milestone payments based on the achievement of development and regulatory milestones for the drug and royalty payments based on sales of the drug. Isis recorded a portion of the upfront payment as research and development revenue during 2001 with the balance to be recognized over the period of Isis' continued involvement under the agreement. For the year ended December 31, 2001, Isis recorded $4,367,000 in total revenue, which was included in the statement of operations as research and development revenues under collaborative agreements.

In May 2001, Isis and Hybridon, Inc. entered into an agreement 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. Additionally, 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 issue Hybridon $19.5 million in Isis common stock before May 2003 subject to certain acceleration clauses triggered by the Company's stock price. In return for access to Isis' patents, Hybridon agreed to issue Isis $6 million in Hybridon common stock before May 2004 also subject to acceleration tied to Hybridon's common stock price. In 2001, Isis issued 857,143 shares of common stock, valued at $15 million, in accordance with this agreement. Isis' balance sheet at December 31, 2001 reflected a licensing asset, net of amortization, of $27.4 million related to this agreement, and a net receivable from Hybridon of $1,500,000.

In July 2001, Celera and Isis' GeneTrove division entered into a collaboration to identify the biological role of more than 200 genes. Celera has the right to select for study a portfolio of genes, from which Celera can further select a limited number of genes for its exclusive use. The data for the remainder of the genes will be included in Isis' human gene function database. Isis retains the rights to develop and commercialize antisense drugs to genes in the collaboration. Celera has agreed to pay Isis research fees for this 18-month collaboration. Revenue from this collaboration was included in the statement of operations as research and development revenues under collaborative agreements.

In August 2001, Isis licensed to Lilly LY900003 (ISIS 3521), a non small-cell lung cancer drug in Phase III trials. In addition to the license of LY900003 (ISIS 3521), the companies have formed a four-year collaboration to discover antisense drugs for metabolic and inflammatory diseases. As part of this collaboration, the companies will use GeneTrove's antisense technology to determine the functional role of up to 1,000 genes. Lilly committed more than $200 million in funding to Isis over a four-year period comprised of the following:

- Lilly made a $75 million equity investment in Isis through the purchase of 4,166,667 shares of common stock at $18 per share.
-

Lilly paid Isis $25 million in upfront fees for LY900003 (ISIS 3521).

- Additionally, the Company recorded $9.2 million in revenue related to reimbursement of cost incurred for the Phase III LY900003 (ISIS 3521) trial, which was included in the statement of operations as research and development revenues under collaborative agreements.

- Lilly committed to loan Isis up to $100 million, interest-free and repayable in cash or stock at $40 per share at the end of the four-year term, to fund the research collaboration.

During the year ended December 31, 2001, Isis recognized revenue of $407,000 related to the research collaboration.

In October 2001, Ibis Therapeutics, a division of Isis, received a two-year contract with the Defense Advanced Research Projects Agency to develop a sensor to detect infectious agents used in biological warfare attacks. Under this two-year contract Isis expects to receive up to $8.9 million for the research program Triangulation Identification Genetic Evaluation of biological Risks. Ibis will work with Science Applications International Corporation, SAIC on this project. Revenue is recognized as expenses are incurred related to the collaboration. For the year ended December 31, 2001, Isis recorded $1,795,000 in total revenue, which was included in the statement of operations as research and development revenues under collaborative agreements.

In November 2001, Isis established a drug development collaboration with OncoGenex Technologies Inc., a Canadian oncology-focused research and development company, to co-develop and commercialize OGX-011, an anti-cancer antisense drug candidate. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target, clusterin, with our proprietary second-generation antisense chemistry. Under the agreement, Isis will conduct preclinical toxicology and

pharmacokinetic studies of OGX-011. Isis will manufacture OGX-011 for preclinical and Phase I/II studies. OncoGenex has responsibility to perform Phase I/II clinical trials to assess the safety and efficacy of OGX-011 as a single agent and in combination with standard chemotherapy in men with localized and hormone refractory prostate cancer. Revenue from this collaboration was included in the statement of operations as research and development revenues under collaborative agreements.

In December 2001, Isis initiated a three-year collaboration with Amgen to discover new antisense drugs. Amgen can develop and commercialize antisense drugs resulting from the collaboration. If drugs from the collaboration are successful, Isis will receive milestone payments upon key clinical and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. Revenue from this collaboration was included in the statement of operations as research and development revenues under collaborative agreements.

In December 2001, Isis licensed to Antisense Therapeutics Limited, an Australian company, ISIS 107248, an antisense inhibitor. In addition, Isis and ATL agreed to participate in a five-year antisense drug discovery and development collaboration, which includes the use of GeneTrove's gene functionalization services. Under the terms of the agreement Isis received, upon the completion of ATL's initial public offering in December 2001, 14% of ATL's common stock. In total, Isis received 30,000,000 common shares and 20,000,000 options upon completion of ATL's IPO. The Company valued its 14% ownership at $2.8 million based on ATL's IPO, and will recognize the amount as revenue over the term of the agreement. The Company is accounting for its holding in ATL as a long-term investment. For the year ended December 31, 2001, Isis recorded $46,000 as revenue, which was included in the statement of operations as research and development revenues under collaborative agreements.

In December 2001, Isis established a supply agreement with Integrated DNA Technologies, Inc., or IDT, which provides for IDT to manufacture antisense inhibitors and research reagents to Isis' specifications. Isis paid IDT $5 million toward future purchases of supplies and expanded its existing licensing agreement on certain antisense patents allowing Isis to exclusively sublicense these patents for functional genomics purposes. The agreement also eliminated milestone payments and reduced royalty rates to be paid to IDT by Isis for commercialized second-generation antisense drugs. Isis paid IDT $3.5 million in 2001 and will pay IDT $1.4 million over the next four years for the license. At December 31, 2001, Isis' balance sheet reflected a deposit and a licensing asset, net of amortization, of $5 million and $3.5 million, respectively.

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., a privately held company, certain Isis patents necessary for Eyetech to develop, make and commercialize EYE001, a non-antisense compound intended for use in the treatment of ophthalmic diseases. EYE001 is currently in Phase II/III clinical trials sponsored by Eyetech. Under the transaction, Eyetech agreed to pay Isis a $2 million license fee, in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis. Additionally, Eyetech agreed to pay milestones and royalties based on the success of EYE001. Isis has no further obligations under the agreement.

In December 2001, Isis' GeneTrove division initiated a functional genomics collaboration with Amgen. Under the terms of the agreement, Isis is performing gene functionalization and target validation services to help Amgen validate and prioritize genes for its drug discovery program. As part of the collaboration, Isis also granted Amgen a license to specific patents covering the Ribonuclease H, or Rnase H, mechanism of action for its in-house antisense based functional genomics program. Revenue from this collaboration was included in the statement of operations as research and development revenues under collaborative agreements.

In December 2001, Isis' GeneTrove division initiated a functional genomics collaboration with Chiron Corporation. Under the terms of the agreement, Isis is performing gene functionalization and target validation services to help Chiron validate and prioritize genes for its drug discovery program. As

part of the collaboration, Isis also granted Chiron a license to specific patents covering the Ribonuclease H, or Rnase H, mechanism of action for its in-house antisense based functional genomics program. Revenue from this collaboration was included in the statement of operations as research and development revenues under collaborative agreements.

7. Restructuring

In December 1999, the unexpected failure of the Company's Phase III clinical trial of ISIS 2302 for the treatment of Crohn's disease prompted a restructuring of the Company. In January 2000, the Company announced a restructuring plan to reduce expenses and focus resources on the development of antisense drugs with significant commercial potential. The estimated cost of restructuring activities was recorded in the first quarter of 2000, and totaled $1.6 million. Actual restructuring costs were primarily related to the Company's elimination of approximately 140 positions during the first four months of 2000. These positions were from all departments of the Company. For the year ended December 31, 2000, the Company incurred total restructuring costs of $1.6 million.

8. 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 ($11,000 for 2001). The Company made approximately $295,000 in matching contributions for the year ended December 31, 2001. The Company did not provide matching contributions under its 401(k) plan in 2000.

9. Affiliate Supplementary Disclosure

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounts for its investment in Orasense under the equity method of accounting. At inception, Elan granted to Orasense a license to its intellectual property for $15 million. The term of the license is 3 years and amortization expense related to this license totaled $5 million for years ended December 31, 2001 and 2000. Orasense has incurred research and development expenses performed by Elan and the Company on its behalf in the course of its product development. The following table presents summary financial

information (in thousands, except per share amounts) for Orasense as of and for the year ended December 31:

	2001	2000
Balance Sheet:		
Assets		
Cash and cash equivalents	$ 11	$ 10
Licenses	1,250	6,250
Total assets	$ 1,261	$ 6,260
Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ 2,097	$ 1,207
Other current liabilities	—	17
Common stock, $1.00 par value; 12,000 authorized, issued and outstanding at December 31, 2001 and 2000	12	12
Additional paid-in capital	33,170	26,178
Accumulated deficit	(34,018)	(21,154)
Total liabilities and stockholders' equity	$ 1,261	$ 6,260
Results of Operations:		
Revenues	$ —	$ —
Research and development expenses	7,864	7,156
Amortization of acquired license	5,000	5,000
Total operating expenses	12,864	12,156
Net loss	$ (12,864)	$ (12,156)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounts for its investment in HepaSense under the equity method of accounting. At inception, Elan granted to HepaSense a license to its intellectual property for $15 million. The term of the license is 3 years and amortization expense related to this license totaled $5 million for years ended December 31, 2001 and 2000. HepaSense has incurred research and development expenses performed by Elan and the Company on its behalf in the course of its product development. The following table presents summary

financial information (in thousands, except per share amounts) for HepaSense as of and for the years ended December 31:

	2001	2000
Balance Sheet:		

Assets		
Cash and cash equivalents	$ 4	$ 1
Licenses	5,000	10,000
Total assets	$ 5,004	$ 10,001
Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ 2,551	$ 481
Other current liabilities	—	30
Common stock, $1.00 par value; 6,001 shares authorized, issued and outstanding at December 31, 2001 and 2000	6	6
Series A Preferred stock, $1.00 par value; 6,000 shares authorized, issued and outstanding at December 31, 2001 and 2000	6	6
Additional paid-in capital	20,558	17,278
Accumulated deficit	(18,117)	(7,800)
Total liabilities and stockholders' equity	$ 5,004	$ 10,001
Results of Operations:		
Revenues	$ —	$ —
Research and development expenses	5,317	2,800
Amortization of acquired license	5,000	5,000
Total operating expenses	10,317	7,800
Net loss	$ (10,317)	$ (7,800)

10. 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, 2001, 2000 and 1999 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2001 Quarters				
Revenues	$ 4,633	$ 7,592	$ 19,304	$ 21,744
Operating expenses	21,867	24,056	24,011	29,441
Loss from operations	(17,234)	(16,464)	(4,707)	(7,697)
Net loss	(22,847)	(23,043)	(12,317)	(15,625)
Accretion of dividends on preferred stock	(319)	(323)	(326)	(331)
Net loss applicable to common stock	$ (23,166)	$ (23,366)	$ (12,643)	$ (15,956)
Basic and diluted net loss per share (1)	$ (0.58)	$ (0.58)	$ (0.29)	$ (0.31)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2000 Quarters				
Revenues	$ 4,054	$ 6,985	$ 18,280	$ 7,936
Operating expenses	16,671	15,160	18,661	17,388
Loss from operations	(12,617)	(8,175)	(381)	(9,452)
Net loss	(18,327)	(14,302)	(5,409)	(15,447)
Accretion of dividends on preferred stock	(281)	(306)	(311)	(316)
Net loss applicable to common stock	$ (18,608)	$ (14,608)	$ (5,720)	$ (15,763)
Basic and diluted net loss per share (1)	$ (0.56)	$ (0.40)	$ (0.15)	$ (0.40)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
1999 Quarters				
Revenues	$ 6,576	$ 7,208	$ 10,638	$ 9,503
Operating expenses	17,131	19,205	18,679	21,969
Loss from operations	(10,555)	(11,997)	(8,041)	(12,466)
Net loss	(12,604)	(16,523)	(12,430)	(17,668)
Accretion of dividends on	—	(117)	(150)	(153)

preferred stock				
Net loss applicable to common stock	$ (12,604)	$ (16,640)	$ (12,580)	$ (17,821)
Basic diluted net loss per share (1)	$ (0.46)	$ (0.59)	$ (0.44)	$ (0.58)

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

QuickLinks

ISIS PHARMACEUTICALS, INC.
10B5-1 TRADING PLAN

This 10b5-1 Trading Plan, (the "Trading Plan"), between ISIS PHARMACEUTICALS, INC. ("Isis") and GOLDEN TRIANGLE SECURITIES LLC ("Broker"), is entered into on February 26, 2002. Capitalized terms not otherwise defined herein will have the meanings given to them in Exhibit A attached hereto.

1. RECITALS.

(a) This Trading Plan is entered into between Isis and Broker for the purpose of establishing a trading plan that complies with the requirements of Rule 10b5-1(c) under the Exchange Act.

(b) The purpose of this Trading Plan is to provide a mechanism by which eligible Sellers can orderly dispose of a portion of each Seller's holdings of Stock, including Stock that such Seller has the right to acquire under the Options.

(c) Isis and Broker hereby agree as follows:

2. APPOINTMENT. Isis hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions set forth below and in the applicable Sellers Plan. Subject to the terms and conditions set forth below, Broker hereby accepts such appointment.

3. SELLERS PLANS. Each Seller may establish up to three individual Sellers Plans with Broker in any Sales Period. In connection with such Sellers Plans, each Seller will establish an account at Broker in the name of and for the benefit of Seller (the "Plan Account"). Sales under each Sellers Plan cannot begin until the Broker receives (i) the Plan Shares, to the extent such Plan Shares are currently owned by Seller, (ii) a properly executed Seller Representation Letter and (iii) a properly completed and executed Sellers Plan, including an acknowledgment by Isis.

4. OBLIGATIONS OF BROKER. With respect to each Sellers Plan, Broker will have the following obligations:

(a) Broker will sell the Plans Shares for the account of each Seller according to the terms of the Seller's Sellers Plan.

(b) Broker will not sell any Stock when broker is in possession of any material nonpublic information concerning Isis or its securities.

(c) Once a Sellers Plan becomes effective, Broker will not allow Seller to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

(d) Broker will withdraw Stock from Seller's Plan Account in order to effect sales of Stock under Seller's Sellers Plan. Broker will exercise Options to effect such sales according to the Seller's Option Priority Guidelines.

(e) Broker will deliver the proceeds from each sale of unrestricted Stock effected under a Sellers Plan to Seller's Account on a normal three-day settlement basis less any commission, commission equivalent, mark-up or differential and other expenses of sale to be paid to Broker. With respect to each sale of restricted Stock, Broker will deliver the net proceeds from such sales as soon as reasonably practicable.

(f) Broker will, in connection with the exercise of Options, remit to Isis the exercise price thereof along with such amounts as may be necessary to satisfy withholding obligations. These amounts will be deducted from the proceeds of the sale of the Stock.

(g) To the extent that any Stock remains in the Plan Account upon termination of the Sellers Plan, Broker agrees to return such Stock promptly to the Seller.

(h) Broker agrees to conduct all sales pursuant to each Sales Plan in accordance with the manner of sale requirement of Rule 144 of the Securities Act and in no event will Broker effect any sale if such sale would exceed the then-applicable amount limitation under Rule 144 or will violate the

"short-swing profit" provisions of Section 16 of the Exchange Act. Broker will file Forms 144 on behalf of Seller as required by applicable law.

(i) Promptly after each Sale, Broker will advise Seller in writing as to the number of shares of Stock sold, the date of each sale and the sales price.

(j) Broker will suspend or terminate a Sellers Plan and cancel any pending sale upon notice from Isis of a Suspension Event (such notice to specify termination or suspension of the Sellers Plan). In the event of a suspension, Broker will cancel any open orders for sales of Plan Shares and will cease placing orders for Sales of Plan Shares under the Sellers Plan until Broker receives written notice from Isis stating that the relevant Suspension Event is no longer in effect. Upon Broker's receipt of notice from Isis, Broker may resume placing orders for sales of the Plan Shares in accordance with the terms and conditions of this Trading Plan and the applicable Sellers Plan; PROVIDED, HOWEVER, that Broker will not reinstate any orders cancelled due to a suspension and will not place any orders that would have been placed during the suspension.

(k) Broker will not sell more than an aggregate of 30,000 shares on any single Trading Day for any individual Seller under all the Sellers Plans established by such Seller. Notwithstanding the foregoing, Broker may sell more than this specified limit if (i) such sale is reasonably necessary to facilitate the exercise of Options that will expire within three Trading Days of such sale and (ii) the Company's Chief Financial Officer has authorized such a trade according to the notice provisions below.

5. TERMINATION; AMENDMENT.

(a) TRADING PLAN. This Trading Plan may be Terminated by Isis at any time upon written notice to Broker. The parties hereto may amend this Trading Plan in writing by mutual written agreement.

(b) VOLUNTARY TERMINATION OF SELLERS PLAN. Seller may terminate a Sellers Plan only during the last five Trading Days of a Sales Period by providing Broker and Isis advance written notice. The terminations will become effective on September 30 of the Sales Period in which proper termination notice was given.

(c) AUTOMATIC TERMINATION OF SELLERS PLAN. An applicable Sellers Plan will automatically terminate on any of the following dates: (i) the date Broker is required to terminate the Sellers Plan under Section 4(j) of this Trading Plan, (ii) the 90th day following the date Broker receives notice of the death of the Seller or of Seller's termination from Isis, (iii) the date Isis or any other entity publicly announces a tender or exchange offer with respect to the Stock or a merger or acquisition of Isis, or (iv) the date Broker receives notice of the commencement or impending commencement of any proceeding relating to or triggered by Seller's bankruptcy or insolvency.

(d) TERMINATION FOR BREACH. Isis may terminate a Sellers Plan immediately upon the breach of a representation or covenant contained in the applicable Seller's Seller Representation Letter.

(e) NO AMENDMENT OF SELLERS PLAN. Seller may not amend a Sellers Plan.

6. GENERAL.

(a) The prices and share amounts set forth in this Trading Plan and in each Sellers Plan will be automatically adjusted on a proportionate basis to take into account any stock split, stock dividend or any change in the capitalization similarly affecting the Stock of the Isis that occurs during the Sales Period.

(b) This Trading Plan, including exhibits, constitutes the entire agreement between the parties with respect to this Trading Plan and supercedes any prior agreements or understandings between the parties with regard to the Trading Plan.

(c) Any notice required to be given under this Trading Plan or a Sellers Plan will be addressed to the relevant party at the address set forth below.

To Broker: Golden Triangle Securities LLC
PO Box 222298
Carmel, CA 93923

Attn: Steve Holber and Peter Albano
Fax: (831) 626-5575
Phone: (831) 626-5570

To Isis: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

Attn: Executive Vice President
Fax: 760-931-3861
Phone: 760-603-2707

with copies to: Linda Powell
Fax: 760-603-3820

To Seller: The contact information specified in the applicable Seller Representation Letter.

Notice will be deemed sufficiently given for all purposes upon the earlier of: (a) the date of actual receipt; (b) if mailed, three (3) calendar days after the date of postmark; (c) if delivered by overnight courier, the next business day such overnight courier regularly makes deliveries; or (d) if sent by facsimile, when the sender's facsimile system generates a message confirming successful transmission of the total number of pages of the notice unless, within one business day after the transmission, the recipient informs the sender that the recipient has not received the entire notice.

(d) This Trading Plan may be signed in counterparts, each of which will be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument.

(e) If any provision of this Trading Plan is or becomes inconsistent with any applicable present or future law, rule or regulation, that provision will be deemed modified or, if necessary, rescinded in order to comply with the relevant law, rule or regulation. All other provisions of this Trading Plan will continue and remain in full force and effect.

(f) This Trading Plan and any Sellers Plan is not an employment contract and nothing in such plans will create in any way whatsoever any obligation on a Seller's part to continue in the employ of Isis, or of Isis to continue Seller's employment with Isis.

(g) In the event of any conflict between the provisions of a Sellers Plan and those of this Trading Plan, the provisions of this Trading Plan will control.

(h) The parties' rights and obligations under this Trading Plan will bind and inure to the benefit of their respective successors, heirs, executors, and administrators and permitted assigns.

IN WITNESS WHEREOF, the undersigned have entered into this Trading Plan as of the date first written above.

ISIS PHARMACEUTICALS, INC.

/s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President

GOLDEN TRIANGLE SECURITIES LLC

/s/ STEVEN HOLBER

Steven Holber
President

EXHIBIT A
DEFINITIONS

"Daily Sales Amount" has the meaning set forth in the applicable Sellers Plan.

"Effective Date" means, with respect to a Sellers Plan, the date the Seller Representation Letter was executed by Seller and accepted by Broker.

"Exchange Act" means the Securities Exchange Act of 1934, as amended.

"Options" means the outstanding stock options issued by Isis listed in the applicable Sellers Plan.

"Option Priority Guidelines" has the meaning set forth in the applicable Sellers Plan.

"Minimum Sales Price" has the meaning set forth in the applicable Sellers Plan.

"Plan Shares" means (i) the Stock and (ii) the Stock issuable upon exercise of the Options, to be sold pursuant to the Sellers Plan.

"Rule 144" means Rule 144 under the Securities Act.

"Sales Period" The first Sales Period will begin on the effective date of this Trading Plan and will end on September 30, 2002. Thereafter, Sales Periods will begin every year on October 1 (beginning with October 1, 2002) and will end on September 30 of the following year until this Trading Plan or the applicable Sellers Plan is terminated.

"Sellers Plan" means a Sellers Plan in the form attached hereto as Exhibit B entered into between Broker and a Seller.

"Securities Act" means the Securities Act of 1933, as amended.

"Seller Representation Letter" is the seller representation letter, a form of which is attached hereto as Exhibit C.

"Seller" means Isis' executive officers, members of its Board of Directors and other individuals specified by Isis who participate in the Trading Plan and who have agreed to only sell Stock under the Trading Plan.

"Stock" means the common stock, $0.001 par value per share, of Isis.

"Suspension Event" means a legal, contractual or regulatory restriction that is applicable to Seller or Seller's affiliates that does not permit the execution of sales made under a Sellers Plan (other than any such restriction relating to Seller's possession or alleged possession of material nonpublic information about Isis or its securities subsequent to the execution of the Sellers Plan), including, without limitation, (i) any restriction related to a merger or acquisition, (ii) a stock

offering requiring an affiliate lock-up, that would prohibit any sale pursuant to the Trading Plan, or (iii) a potential violation of Section 16 of the Exchange Act.

"Trading Day" means any day during the Sales Period that the Nasdaq Stock Market is open for business and the Stock trades regularly on such day.

EXHIBIT B

SELLERS PLAN

EFFECTIVE DATE: _____

SELLER'S NAME: _____

SELLER'S ACCOUNT NUMBER: _____

COMMISSIONS:

PLAN SHARES:

_____ shares of Stock owned by Seller; and

_____ shares of Stock issuable upon the exercise of the Options listed on the last page of this Sellers Plan.

OPTION PRIORITY GUIDELINES:

(PLEASE CHECK ONLY ONE OF THE FOLLOWING)

| | Exercise first those Options with the earliest expiration date; or

| | Exercise first those Options with the lowest exercise price.

(PLEASE CHECK ONLY ONE OF THE FOLLOWING)

| | To complete sales under this Sellers Plan, Broker will sell the Plan Shares owned by Seller first, before exercising any Options (except if such Options are about to expire); or

| | To complete sales under this Sellers Plan, Broker will sell the shares issuable upon exercise of the Options first, before selling the Plan Shares owned by Seller.

IN THE EVENT THAT UNEXERCISED OPTIONS ARE ABOUT TO EXPIRE, BROKER WILL EXERCISE SUCH OPTIONS ON OR BEFORE THE LAST TRADING DAY PRIOR TO THE EXPIRATION DATE OF THE OPTIONS.

Broker will in no event exercise any Option if at the time of exercise the exercise price of the Option is equal to or higher than then current market price of the Stock.

INSTRUCTIONS:

During the Sales Period, Broker will sell the Daily Sales Amount, if any, for the account of Seller on each Trading Day under ordinary principles of best execution at the then-prevailing market price; provided that Broker will not sell any shares of Stock under a Sellers Plan at a price of less than the Minimum Sales Price.

If, consistent with ordinary principles of best execution, Broker cannot sell the Daily Sales Amount on any Trading Day, then the amount of such shortfall may be sold as soon as practicable on the immediately succeeding Trading Day and on each subsequent Trading Day as is necessary to sell such shortfall consistent with the ordinary principals of best execution. If any shortfall exists after the close of trading on the last Trading Day prior to the termination of this Trading Plan or the applicable Sellers Plan, Broker's obligation and authorization to sell such shares will terminate.

MINIMUM SALES PRICE:

| | $_____ per share (before deducting any commission, commission equivalent, mark-up or differential and other expenses of sale); or

| | The greater of (i) the 20-day trailing average closing sale price of the Stock, as reported by Bloomberg (or, if such trailing average price is not reported by Bloomberg, the 20-day trailing average closing sale price as calculated by Broker, whose calculation shall be final and binding absent gross error), or (ii) $_____ per share (before deducting any commission, commission equivalent, mark-up or differential and other expenses of sale); or

| | For each number of shares listed on the table below, the Minimum Sales Price will be the price opposite such number of shares.

- ----

NUMBER OF SHARES

MINIMUM SALES PRICE

DAILY SALES AMOUNT (PLEASE CHECK ONLY ONE OF THE FOLLOWING):

| | Broker will set the Daily Sales Amount in its sole discretion; or

| | _____ shares of Stock; or

| | an amount of Stock resulting in aggregate proceeds (after deducting any commission, commission equivalent, mark-up or differential, other expenses of sale, exercise prices (if any), withholding taxes and other expenses of exercise) of $_____; or

| | _____ shares of Stock, EXCEPT if _____ or more shares of Stock have been sold under this Sellers Plan within the _____ days preceding the current Trading Day, then the Daily Sales Amount will be zero shares.

RELOAD FEATURE

| | On the first day of each Sales Period, unless this Sellers Plan is otherwise terminated, new shares of stock will be added as Plan Shares to this Sellers Plan equal to the greater of (i) the number of Plan Shares in the preceding Sales Period minus any shares not sold pursuant to the Sellers Plan during the preceding Sales Period or (ii) the number of shares of Stock subject to stock options held by Seller that will expire during the then current Sales Period. If necessary to reload the Plan Shares (as described above), the Options will be updated to add the earliest to expire stock options of the Seller until the Plan Shares have been reloaded. Notwithstanding the foregoing, Options will not be added to this Sellers Plan that will not vest within the then current Sales Period.

OTHER INSTRUCTIONS:

- _____

- _____

- _____

- _____

- _____

- _____

- _____

- _____

- _____

- _____

EXHIBIT C
SELLER REPRESENTATION LETTER
SELLER REPRESENTATION AND COVENANT LETTER

Date: _____

Golden Triangle Securities LLC
PO Box 222298
Carmel, CA 93923
Attn: Steve Holber

Dear Steve:

In consideration of your accepting orders to sell the Stock of Isis Pharmaceuticals, Inc. ("Isis") under the Isis Pharmaceuticals 10b5-1 Trading Plan (the "Trading Plan") and the Sellers Plan (as defined below), the Seller makes the representations and agrees to the covenants set forth below.

All capitalized terms that are not otherwise defined herein shall have the meanings ascribed to them in the Trading Plan. The terms of the Trading Plan are incorporated herein by reference. In the event of any conflict between the provisions of this letter and the Trading Plan, the provisions of the Trading Plan will control.

Seller hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions of the Trading Plan and the Sellers Plan attached hereto and incorporated herein by reference as Exhibit I (the "Sellers Plan"). Broker hereby accepts such appointment.

SELLER REPRESENTATIONS.

7. Sales of Stock under the Sellers Plan have been approved by an authorized representative of Isis.

8. As of the date hereof, Seller is not aware of any material nonpublic information concerning Isis or its securities. Seller is entering into the Sellers Plan in good faith and not as part of a plan or scheme to evade compliance with the federal securities laws.

9. The Stock to be sold under the Sellers Plan is owned free and clear by Seller (subject, in the case of shares underlying Options, only to the compliance by Seller with the exercise provisions of such options) and is not subject to any agreement granting any pledge, lien, mortgage, hypothecation, security interest, charge, option or encumbrance or any other limitation on disposition, other than those which may have been entered into between Seller and Broker or imposed by Rules 144 or 145 under the Securities Act.

10. Seller has had an opportunity to discuss the Sellers Plan with his or her own advisors as to the legal, tax, business, financial and related aspects of the Sellers Plan and has determined that the Sellers Plan meets the affirmative defense criteria set forth in Rule 10b5-

1(c). Seller has not relied upon Broker or Isis (or any person affiliated with Broker or Isis) in connection with, Seller's adoption and implementation of the Sellers Plan.

11. Seller acknowledges and agrees that, once the Sellers Plan becomes effective, Seller does not have, and shall not attempt to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

SELLER COVENANTS.

12. While the Sellers Plan is in effect, Seller agrees not to (i) sell any securities of Isis outside of the transactions contemplated by the Trading Plan, (ii) enter into or alter any corresponding or hedging transaction or position with respect to the Stock covered by the Sellers Plan (including, without limitation, with respect to any securities convertible or exchangeable into the Stock), and (iii) alter or deviate from the terms of the Sellers Plan.

13. Seller agrees to deliver to Broker the Plan Shares pursuant to the Sellers Plan to be placed into Seller's Plan Account prior to the commencement of sales under the Sellers Plan.

14. Seller agrees to make appropriate arrangements with Isis and its transfer agent and stock plan administrator to permit Broker to furnish notice to Isis of the exercise of the Options and to have underlying shares delivered to Broker as necessary to effect sales under the Sellers Plan. Seller hereby authorizes Broker to serve as Seller's agent and attorney-in-fact and, in accordance with the terms of the Sellers Plan, to exercise the Options. Seller agrees to complete, execute and deliver to Broker cashless exercise forms, in sufficient form to allow for the exercise of Options pursuant to the Sellers Plan at such times and in such numbers as Broker may reasonably request.

15. Seller will not, directly or indirectly, communicate any information relating to the Stock or Isis to any employee of Broker or its affiliates who is involved, directly or indirectly, in executing the Sellers

Plan at any time while the Sellers Plan is in effect.

16. Seller agrees to notify Broker's compliance office by telephone or facsimile as soon as practicable if Seller becomes aware of the occurrence of any Suspension Event. Such notice will indicate the anticipated duration of the restriction, but will not include any other information about the nature of the restriction or its applicability to Seller and will not in any way communicate any material nonpublic information about Isis or its securities to Broker.

17. Seller understands and agrees that so long as it is an "affiliate" of Isis for purposes of Rule 144 under the Securities Act, all sales under the Plan will be in accordance with Rule 144. Seller agrees not to take any action that would cause Seller to aggregate sales under the Sellers Plan with sales of other securities of the issuer pursuant to Rule 144, and not to take any action that would cause the sales under the Plan not to comply with Rule 144.

18. Seller agrees to complete, execute and deliver to Broker Forms 144 for the sales to be effected under the Sellers Plan at such times and in such numbers as Broker reasonably requests. The "Remarks" section of each Form 144 will state that the sale is being made pursuant to a previously adopted plan intended to comply with Rule 10b5-1(c) and will indicate the date the Sellers Plan was adopted and that the representation is made as of such date.

19. Seller agrees to make all filings, if any, required under Sections 13(d), 13(g) and 16 of the Exchange Act in a timely manner, to the extent any such filings are applicable to Seller.

20. Seller agrees that Seller will at all times during the Sales Period, in connection with the performance of the Sellers Plan, comply with all applicable laws, including, without limitation, Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

21. Seller will notify Broker and Isis of any other purchase or sale transactions involving securities of Isis that are not contemplated by the Trading Plan.

Very truly yours,

[name]
[address]
[telephone]
[fax]

AGREED:

Golden Triangle Securities LLC

- ---

Steven Holber
President

ACKNOWLEDGED:

Isis Pharmaceuticals, Inc.

_____

B. Lynne Parshall
Executive Vice President

ISIS PHARMACEUTICALS, INC.

2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001
APPROVED BY STOCKHOLDERS _____, 2002
EFFECTIVE DATE: _____, 2002

1. PURPOSES.

(a) AMENDMENT AND RESTATEMENT. This Plan is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.

(b) ELIGIBLE OPTION RECIPIENTS. The persons eligible to receive Options are the Non-Employee Directors of the Company.

(c) AVAILABLE OPTIONS. The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Nonstatutory Stock Options.

(d) GENERAL PURPOSE. The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

(a) "AFFILIATE" means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.

(b) "ANNUAL GRANT" means an Option granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.

(c) "BOARD" means the Board of Directors of the Company.

(d) "CAPITALIZATION ADJUSTMENT" has the meaning ascribed to that term in Section 11(a).

(e) "CHANGE IN CONTROL" means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

Notwithstanding the foregoing, a Change in Control shall not be deemed to occur solely because the level of Ownership held by any Exchange Act Person (the "Subject Person") exceeds the percentage threshold specified above of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, provided that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities (other than through a purchase directly from the Company) that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the percentage threshold specified above, then a Change in Control shall be deemed to occur.

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in

such merger, consolidation or similar transaction or more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction;

(iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur;

(iv) there is consummated a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than 50% of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date this Plan is adopted by the Board, are members of the Board (the "Incumbent Board") cease for any reason to constitute at least a majority of the members of the Board; (PROVIDED, HOWEVER, that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board).

Notwithstanding the foregoing or any other provision of this Plan, the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Optionholder shall supersede the foregoing definition with respect to Options subject to such agreement (it being understood, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply).

(f) "CODE" means the Internal Revenue Code of 1986, as amended.

(g) "COMMON STOCK" means the common stock of the Company.

(h) "COMPANY" means Isis Pharmaceuticals, Inc., a Delaware corporation.

(i) "CONSULTANT" means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) serving as a member of the Board of Directors of an Affiliate and who is compensated for such services. However, the term "Consultant" shall not include Directors who are not compensated by the Company for their services as Directors, and the payment of a director's fee by the Company for services as a Director shall not cause a Director to be considered a "Consultant" for purposes of the Plan.

(j) "CONTINUOUS SERVICE" means that the Optionholder's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Optionholder renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Optionholder renders such service, provided that there is no interruption or termination of the Optionholder's service with the Company or an Affiliate, shall not terminate an Optionholder's Continuous Service. For example, a change in status from a Non-Employee Director of the Company to a Consultant of an Affiliate or an Employee of the Company shall not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

(k) "CORPORATE TRANSACTION" means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;

(iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(l) "DIRECTOR" means a member of the Board of Directors of the Company.

(m) "DISABILITY" means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

(n) "EMPLOYEE" means any person employed by the Company or an Affiliate. Service as a Director or payment of a director's fee by the Company or an Affiliate shall not be sufficient to constitute "employment" by the Company or an Affiliate.

(o) "ENTITY" means a corporation, partnership or other entity.

(p) "EXCHANGE ACT" means the Securities Exchange Act of 1934, as amended.

(q) "EXCHANGE ACT PERSON" means any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that "Exchange Act Person" shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.

(r) "FAIR MARKET VALUE" means, as of any date, the value of the Common Stock determined as follows:

(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.

(ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.

(s) "INITIAL GRANT" means an Option granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.

(t) "NON-EMPLOYEE DIRECTOR" means a Director who is not an Employee.

(u) "NONSTATUTORY STOCK OPTION" means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(v) "OFFICER" means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

(w) "OPTION" means a Nonstatutory Stock Option granted pursuant to the Plan.

(x) "OPTION AGREEMENT" means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an individual Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(y) "OPTIONHOLDER" means a person to whom an Option is granted

pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(z) "OWN," "OWNED," "OWNER," "OWNERSHIP" A person or Entity shall be deemed to "Own," to have "Owned," to be the "Owner" of, or to have acquired "Ownership" of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(aa) "PLAN" means this Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, which is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.

(bb) "RULE 16b-3" means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(cc) "SECURITIES ACT" means the Securities Act of 1933, as amended.

(dd) "SUBSIDIARY" means, with respect to the Company, (i) any corporation of which more than 50% of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly Owned by the Company, and (ii) any partnership in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than 50%.

3. ADMINISTRATION.

(a) ADMINISTRATION BY BOARD. The Board shall administer the Plan. The Board may not delegate administration of the Plan to a committee.

(b) POWERS OF BOARD. The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine the provisions of each Option to the extent not specified in the Plan.

(ii) To construe and interpret the Plan and Options granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Option Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

(iii) To amend the Plan or an Option as provided in Section 12.

(iv) To terminate or suspend the Plan as provided in Section 13.

(v) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan.

(c) EFFECT OF BOARD'S DECISION. All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(d) ARBITRATION. Any dispute or claim concerning any Option granted (or not granted) pursuant to the Plan or any disputes or claims relating to or arising out of the Plan shall be fully, finally and exclusively resolved by binding arbitration conducted pursuant to the Commercial Arbitration Rules of the American Arbitration Association in San Diego, California. The Company shall pay all arbitration fees. In addition to any other relief, the arbitrator may award to the prevailing party recovery of its attorney's fees and costs. By accepting an Option, Optionholders and the Company waive their respective rights to have any such disputes or claims tried by a judge or jury.

4. SHARES SUBJECT TO THE PLAN.

(a) SHARE RESERVE. Subject to the provisions of Section 11(a) relating to Capitalization Adjustments, the Common Stock that may be issued

pursuant to Options shall not exceed in the aggregate 600,000 shares of Common Stock.

(b) REVERSION OF SHARES TO THE SHARE RESERVE. If any Option shall for any reason expire or otherwise terminate, in whole or in part, without having been exercised in full, the shares of Common Stock not acquired under such Option shall revert to and again become available for issuance under the Plan.

(c) SOURCE OF SHARES. The shares of Common Stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

5. ELIGIBILITY.

The Options as set forth in Section 6 of the Plan automatically shall be granted under the Plan to all Non-Employee Directors.

6. NON-DISCRETIONARY GRANTS.

(a) INITIAL GRANTS. Without any further action of the Board, each person who is elected or appointed for the first time after the effective date of this amendment and restatement of the Plan to be a Non-Employee Director automatically shall, upon the date of his or her initial election or appointment to be a Non-Employee Director by the Board or stockholders of the Company, as applicable, be granted an Initial Grant to purchase 20,000 shares of Common Stock on the terms and conditions set forth herein.

(b) ANNUAL GRANTS. Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2002, each person who is

then a Non-Employee Director automatically shall be granted an Annual Grant to purchase 10,000 shares of Common Stock on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day.

7. OPTION PROVISIONS.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. Each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) TERM. No Option shall be exercisable after the expiration of 10 years from the date it was granted.

(b) EXERCISE PRICE. The exercise price of each Option shall be 100% of the Fair Market Value of the Common Stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option may be granted with an exercise price lower than that set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) CONSIDERATION. The purchase price of Common Stock acquired pursuant to an Option shall be paid in cash at the time the Option is exercised.

(d) TRANSFERABILITY. An Option will not be transferable except as determined by the Board.

(e) EXERCISE SCHEDULE. The Option shall be exercisable as the shares of Common Stock subject to the Option vest.

(f) VESTING SCHEDULE. The Option shall vest and become exercisable as follows:

(i) Initial Grants: one-fourth of the shares subject to the Option shall vest on each annual anniversary of the date of grant provided that the Optionholder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(ii) Annual Grants: one-fourth of the shares subject to

the Option shall vest on each annual anniversary of the date of grant provided that the Optionholder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(g) TERMINATION OF CONTINUOUS SERVICE. In the event that an Optionholder's Continuous Service terminates (other than upon the Optionholder's death or Disability), the

Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date 3 months following the termination of the Optionholder's Continuous Service (or such longer or shorter period specified in the Option Agreement), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Optionholder does not exercise his or her Option within the time specified in the Option Agreement, the Option shall terminate.

(h) EXTENSION OF TERMINATION DATE. An Optionholder's Option Agreement may also provide that if the exercise of the Option following the termination of the Optionholder's Continuous Service (other than upon the Optionholder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Optionholder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements.

(i) DISABILITY OF OPTIONHOLDER. In the event that an Optionholder's Continuous Service terminates as a result of the Optionholder's Disability, the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination), but only within such period of time ending on the earlier of (i) the date 12 months following such termination (or such longer or shorter period specified in the Option Agreement) or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Optionholder does not exercise his or her Option within the time specified herein, the Option shall terminate.

(j) DEATH OF OPTIONHOLDER. In the event that (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death or (ii) the Optionholder dies within the period (if any) specified in the Option Agreement after the termination of the Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Optionholder's death pursuant to subsection 7(d), but only within the period ending on the earlier of (1) the date 18 months following the date of death (or such longer or shorter period specified in the Option Agreement) or (2) the expiration of the term of such Option as set forth in the Option Agreement. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

8. COVENANTS OF THE COMPANY.

(a) AVAILABILITY OF SHARES. During the terms of the Options, the Company shall keep available at all times the number of shares of Common Stock required to satisfy such Options.

(b) SECURITIES LAW COMPLIANCE. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Options and to issue and sell shares of Common Stock upon exercise of the

Options; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Option or any Common Stock issued or issuable pursuant to any such Option. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency

the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Options unless and until such authority is obtained.

9. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of Common Stock pursuant to Options shall constitute general funds of the Company.

10. MISCELLANEOUS.

(a) ACCELERATION OF EXERCISABILITY AND VESTING. The Board shall have the power to accelerate the time at which an Option may first be exercised or the time during which an Option or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Option stating the time at which it may first be exercised or the time during which it will vest.

(b) STOCKHOLDER RIGHTS. No Optionholder shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Option unless and until such Optionholder has satisfied all requirements for exercise of the Option pursuant to its terms.

(c) NO SERVICE RIGHTS. Nothing in the Plan or any instrument executed or Option granted pursuant thereto shall confer upon any Optionholder any right to continue to serve the Company as a Non-Employee Director or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(d) INVESTMENT ASSURANCES. The Company may require an Optionholder, as a condition of exercising or acquiring Common Stock under any Option, (i) to give written assurances satisfactory to the Company as to the Optionholder's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (ii) to give written assurances satisfactory to the Company stating that the Optionholder is acquiring the Common Stock subject to the Option for the Optionholder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Option has been registered under a then currently effective registration statement under the Securities Act or (2)

as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(e) WITHHOLDING OBLIGATIONS. To the extent provided by the terms of an Option Agreement, the Optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise or acquisition of Common Stock under an Option by any of the following means (in addition to the Company's right to withhold from any compensation paid to the Optionholder by the Company) or by a combination of such means: (i) tendering a cash payment; (ii) authorizing the Company to withhold shares of Common Stock from the shares of Common Stock otherwise issuable to the Optionholder as a result of the exercise or acquisition of Common Stock under the Option, provided, however, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid variable award accounting); or (iii) delivering to the Company owned and unencumbered shares of Common Stock.

11. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) CAPITALIZATION ADJUSTMENTS. If any change is made in, or other

event occurs with respect to, the Common Stock subject to the Plan, or subject to any Option, without the receipt of consideration by the Company (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 the Company) (each, a "Capitalization Adjustment"), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Plan pursuant to subsection 4(a) and to the nondiscretionary Options specified in Section 6, and the outstanding Options will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Options. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) DISSOLUTION OR LIQUIDATION. In the event of a dissolution or liquidation of the Company, then all outstanding Options shall terminate immediately prior to the completion of such dissolution or liquidation.

(c) CORPORATE TRANSACTION. In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Options outstanding under the Plan or may substitute similar options for Options outstanding under the Plan (it being understood that similar options include, but are not limited to, options to acquire the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Options or substitute similar options for such outstanding Options, then with respect

to Options that have been neither assumed nor substituted and that are held by Optionholders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Options (and, if applicable, the time at which such Options may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Options shall terminate if not exercised at or prior to such effective time. With respect to Options outstanding under the Plan that have been neither assumed nor substituted and that are held by Optionholders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Options (and, if applicable, the time at which such Option may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Option, and such Options shall terminate if not exercised prior to the effective time of the Corporate Transaction.

(d) CHANGE IN CONTROL. Notwithstanding any other provisions of the Plan to the contrary, if a Change in Control occurs and the Optionholder's Continuous Service has not terminated prior to the effective date of such Change in Control, then the vesting and exercisability of the shares of Common Stock subject to the Optionholder's Options shall be accelerated in full as of the effective date of the Change in Control. Following such Change in Control (other than a Change in Control resulting from a plan of complete dissolution or liquidation of the Company) and notwithstanding any other provision of the Plan to the contrary and provided that the Optionholder's Continuous Service has not terminated prior to the effective date of the Change in Control, then the Optionholder's Options shall expire on the earliest of (i) 12 months following the effective date of such Change in Control or (ii) the Expiration Date indicated in the Optionholder's Grant Notice.

(e) PARACHUTE PAYMENTS. If any payment or benefit the Optionholder would receive pursuant to a Change in Control from the Company or otherwise ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be reduced to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Optionholder's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits

constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the following order unless the Optionholder elects in writing a different order (PROVIDED, HOWEVER, that such election shall be subject to Company approval if made on or after the effective date of the event that triggers the Payment): reduction of cash payments; cancellation of accelerated vesting of Options or other equity-based awards; reduction of employee benefits. In the event that acceleration of vesting of Options or other equity-based compensation is to be reduced, such acceleration of vesting shall be cancelled in the reverse order of the date of grant

of the Optionholder's Options or other equity-based awards unless the Optionholder elects in writing a different order for cancellation.

The accounting firm engaged by the Company for general audit purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The accounting firm engaged to make the determinations hereunder shall provide its calculations, together with detailed supporting documentation, to the Optionholder and the Company within 15 calendar days after the date on which the Optionholder's right to a Payment is triggered (if requested at that time by the Optionholder or the Company) or such other time as requested by the Optionholder or the Company. If the accounting firm determines that no Excise Tax is payable with respect to a Payment, either before or after the application of the Reduced Amount, it shall furnish the Company and the Optionholder with an opinion reasonably acceptable to the Optionholder that no Excise Tax will be imposed with respect to such Payment. Any good faith determinations of the accounting firm made hereunder shall be final, binding and conclusive upon the Optionholder and the Company.

12. AMENDMENT OF THE PLAN AND OPTIONS.

(a) AMENDMENT OF PLAN. The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 11(a) relating to Capitalization Adjustments, no amendment shall be effective unless approved by the stockholders of the Company to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) STOCKHOLDER APPROVAL. The Board, in its sole discretion, may submit any other amendment to the Plan for stockholder approval.

(c) NO IMPAIRMENT OF RIGHTS. Rights under any Option granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Optionholder and (ii) the Optionholder consents in writing.

(d) AMENDMENT OF OPTIONS. The Board at any time, and from time to time, may amend the terms of any one or more Options; provided, however, that the rights under any Option shall not be impaired by any such amendment unless (i) the Company requests the consent of the Optionholder and (ii) the Optionholder consents in writing.

13. TERMINATION OR SUSPENSION OF THE PLAN.

(a) PLAN TERM. The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on the day before the tenth anniversary of the date the Plan is approved by the stockholders of the Company. No Options may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) NO IMPAIRMENT OF RIGHTS. Suspension or termination of the Plan shall not impair rights and obligations under any Option granted while the Plan is in effect except with the written consent of the Optionholder.

14. EFFECTIVE DATE OF PLAN.

The Plan shall become effective as determined by the Board, but no Option shall be exercised unless and until the Plan has been approved by the stockholders of the Company, which approval shall be within 12 months before or after the date the Plan is adopted by the Board.

15. CHOICE OF LAW.

The law of the State of California shall govern all questions concerning the construction, validity and interpretation of this Plan without regard to such state's conflict of laws rules.

Exhibit 10.42

2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
GRANT NOTICE

Optionee: _____ Date: _____

ISIS PHARMACEUTICALS, INC.
NON-STATUTORY STOCK OPTION AGREEMENT

ISIS PHARMACEUTICALS, INC. (the "Company"), pursuant to its 2002 Non-Employee Directors' Stock Option Plan (the "Plan"), hereby grants to Optionholder an option to purchase the number of shares of the Company's Common Stock set forth below. This option is subject to all of the terms and conditions as set forth herein and in the Stock Option Agreement (Attachment I hereto), the Plan and the Notice of Exercise, all of which are attached hereto and incorporated herein in their entirety.

Number of Shares Subject to Option: _____

VESTING SCHEDULE:

NUMBER OF SHARES (INSTALLMENT)	DATE OF EARLIEST EXERCISE (VESTING)

Exercise Price Per Share: _____ 1 Expiration Date: _____ 2

Isis Pharmaceuticals, Inc.

By: _____ Optionee: _____
Duly authorized on behalf of
the Board of Directors Address:

OPTIONEE:

ADDITIONAL TERMS/ACKNOWLEDGEMENTS: The undersigned Optionholder acknowledges receipt of, and understands and agrees to, this Grant Notice, the Stock Option Agreement and the Plan. Optionholder further acknowledges that as of the Date of Grant, this Grant Notice, the Stock Option Agreement and the Plan set forth the entire understanding between Optionholder and the Company regarding the acquisition of stock in the Company and supersede all prior oral and written agreements on that subject with the exception of (i) options previously granted and delivered to Optionholder under the Plan, and (ii) the following agreements only:

OTHER AGREEMENTS:

_____

_____

1 Not less than 100% of the fair market value of the Common Stock on the date of grant of this option.
2 Less than 10 years from the date of grant of this option.

ISIS PHARMACEUTICALS, INC.
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

STOCK OPTION AGREEMENT
(NONSTATUTORY STOCK OPTION)

Pursuant to your Stock Option Grant Notice ("Grant Notice") and this Stock Option Agreement, Isis Pharmaceuticals, Inc. (the "Company") has granted you an option under its 2002 Non-Employee Directors' Stock Option Plan (the "Plan") to purchase the number of shares of the Company's Common Stock indicated

in your Grant Notice at the exercise price indicated in your Grant Notice. Defined terms not explicitly defined in this Stock Option Agreement but defined in the Plan shall have the same definitions as in the Plan.

The details of your option are as follows:

1. VESTING. Subject to the limitations contained herein, your option will vest as provided in your Grant Notice, provided that vesting will cease upon the termination of your Continuous Service.

2. NUMBER OF SHARES AND EXERCISE PRICE. The number of shares of Common Stock subject to your option and your exercise price per share referenced in your Grant Notice may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

3. METHOD OF PAYMENT. Payment of the exercise price is due in full upon exercise of all or any part of your option. You may make payment of the exercise price in cash or by check.

4. WHOLE SHARES. You may exercise your option only for whole shares of Common Stock.

5. SECURITIES LAW COMPLIANCE. Notwithstanding anything to the contrary contained herein, you may not exercise your option unless the shares of Common Stock issuable upon such exercise are then registered under the Securities Act or, if such shares of Common Stock are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Securities Act. The exercise of your option must also comply with other applicable laws and regulations governing your option, and you may not exercise your option if the Company determines that such exercise would not be in material compliance with such laws and regulations.

6. TERM. You may not exercise your option before the commencement of its term or after its term expires. Unless otherwise provided in Section 11(d) of the Plan, the term of your option commences on the Date of Grant and expires upon the EARLIEST of the following:

(a) 3 months after the termination of your Continuous Service for any reason other than your Disability or death, provided that if during any part of such 3 month period your option is not exercisable solely because of the condition set forth in the preceding paragraph relating to "Securities Law Compliance," your option shall not expire until the earlier of the Expiration

Date or until it shall have been exercisable for an aggregate period of 3 months after the termination of your Continuous Service;

(b) 12 months after the termination of your Continuous Service due to your Disability;

(c) 18 months after your death if you die either during your Continuous Service or within 3 months after your Continuous Service terminates; or

(d) the day before the 10th anniversary of the Date of Grant.

7. EXERCISE.

(a) You may exercise the vested portion of your option during its term by delivering a Notice of Exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require.

(b) The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares equals less than 1,000 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

(c) By exercising your option you agree that, as a condition to any exercise of your option, the Company may require you to enter into an arrangement providing for the payment by you to the Company of any tax withholding obligation of the Company arising by reason of (1) the exercise of your option, (2) the lapse of any substantial risk of forfeiture to which the shares of Common Stock are subject at the time of exercise, or (3) the disposition of shares of Common Stock acquired upon such exercise.

8. TRANSFERABILITY. This option is not transferable except by will or by the laws of descent and distribution, and is exercisable during your lifetime only by you; notwithstanding the foregoing, you may transfer part or all of this option to any of the following:

(i) your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for your benefit or the benefit of your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or,

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, you may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of your death, will thereafter be entitled to exercise the option.

9. RIGHT OF REPURCHASE. To the extent provided in the Company's bylaws as amended from time to time, the Company shall have the right to repurchase all or any part of the shares of Common Stock you acquire pursuant to the exercise of your option.

10. OPTION NOT A SERVICE CONTRACT. Your option is not an employment or service contract, and nothing in your option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company or an Affiliate, or of the Company or an Affiliate to continue your employment. In addition, nothing in your option shall obligate the Company or an Affiliate, their respective stockholders, Boards of Directors, Officers or Employees to continue any relationship that you might have as a Director or Consultant for the Company or an Affiliate.

11. WITHHOLDING OBLIGATIONS. You may not exercise your option unless the tax withholding obligations of the Company and/or any Affiliate are satisfied. Accordingly, you may not be able to exercise your option when desired even though your option is vested, and the Company shall have no obligation to issue a certificate for such shares of Common Stock or release such shares of Common Stock from any escrow provided for herein.

12. NOTICES. Any notices provided for in your option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company.

13. GOVERNING PLAN DOCUMENT. Your option is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your option, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of your option and those of the Plan, the provisions of the Plan shall control.

EXHIBIT 21.1
ISIS PHARMACEUTICALS, INC.

LIST OF SUBSIDIARIES

Isis Pharmaceuticals, Inc has the following subsidiaries:

Name	Organized under the laws of	Percentage of voting securities owned by immediate parent
HepaSense, Ltd.	Bermuda	80.10
Orasense, Ltd.	Bermuda	80.10

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-8 and Form S-3) of Isis Pharmaceuticals, Inc. of our report dated February 1, 2002 with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. included in the Annual Report (Form 10-K) for the year ended December 31, 2001.

/s/ ERNST & YOUNG LLP

San Diego California
March 27, 2002