QuickLinks -- Click here to rapidly navigate through this document

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

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

For the fiscal year ended December 31, 2002

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. ☒

Indicate by check mark whether the Registrant is an accelerated filer (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☒ No 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 $421,911,654 as of June 30, 2002.*

The number of shares of voting common stock outstanding as of February 28, 2003 was 55,381,331.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Registrant's definitive Proxy Statement filed on or about April 25, 2003, with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on June 10, 2003, is incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 61 to 66 incorporates several documents by reference as indicated therein.

* Excludes 9,826,723 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 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.

Vitravene® is a registered trademark of Novartis AG. Taxotere® is a registered trademark of Aventis Pharmaceuticals, Inc. GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc. Affinitak™, a trademark of Eli Lilly and Isis Pharmaceuticals, Inc. HepaSense™ is a trademark of HepaSense Ltd. Orasense™ is a trademark of Orasense Ltd.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company exploiting proprietary RNA-based drug discovery technologies to identify and commercialize novel drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins 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, or oligonucleotides, designed to hybridize, or bind, with high specificity to their RNA target and modulate the production of proteins associated with diseases. With our Ibis technology, we use our expertise in RNA to design small molecule drugs that bind to RNA through mechanisms other than hybridization. We also use our antisense technology in collaborations with pharmaceutical companies to identify and prioritize attractive gene targets for their drug discovery programs. We are a leader 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 and European regulatory requirements and to commercially manufacture antisense drugs. We currently have 12 antisense 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 inflammatory, viral, metabolic and dermatological diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. Physician's may be able to dose our second-generation drugs, which represent over half of our drugs in development, as infrequently as once per month. We are also making progress on developing oral formulations of our second-generation drugs. Recent clinical trial data showed the potential feasibility of oral solid dosage forms for antisense drugs. This oral formulation platform will increase the commercial competitiveness of our antisense drugs in the marketplace and broaden its applicability.

Affinitak, formerly LY900003 or ISIS 3521, is our most advanced product in development. We recently announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in overall survival of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone. Survival was the primary endpoint. The median survival for the Affinitak treated patients was ten months, compared to 9.7 months for those patients treated with the chemotherapy alone. Additional analyses of the data, however, suggest that Affinitak was active in this trial. For example, using an alternative statistical analysis of all 616 patients which considered predefined variables, including duration of treatment, survival of the Affinitak treated patients was greater than that of patients in the control group. This result was statistically significant. Lilly and we are performing an in-depth analysis of the data and expect to submit the complete findings from this trial for scientific presentation at an appropriate medical meeting later this year. Lilly plans to evaluate Affinitak's performance in its on-going Phase III trial, in which patients are being treated with Affinitak in combination with gemcitabine and cisplatin. As we proceed with these evaluations, Lilly and we will make a decision about the future development of Affinitak.

We currently have two Phase III clinical trials for another product, ISIS 2302, or alicaforsen, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America and Europe. We have five additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide important information about the function of genes. We use this information to direct our own drug discovery research and that of our antisense drug discovery partners, such as Lilly and Amgen. We generate this information rapidly and efficiently using the same proprietary methods and systems that we developed to create antisense drugs. We offer anitsense-based gene function information to pharmaceutical company partners that are evaluating the genes as targets for their own drug discovery programs. Through the sale of this informaton, we generate revenue from our research efforts and increase industry experience with our technology. We are currently collaborating with ten major pharmaceutical partners, including Abbott Laboratories, Inc.; Amgen Inc.; Aventis; Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; GlaxoSmithKline plc; Johnson & Johnson Pharmaceutical Research & Development, LLC; Merck & Co., Inc. and Pharmacia Corporation. We also license our antisense-based functional genomics patents to partners. Through these license agreements, GeneTrove partners gain access to our functional genomics suite of patents for use in their internal genomics programs. In August 2001, we added a subscription database product to GeneTrove's offerings. We were unsuccessful in generating customers for our database product and in November 2002 we announced its termination. This resulted in a reorganization of the GeneTrove division and a reduction in its workforce by approximately 25 people. The restructuring plan also provided for the write-down of certain intellectual property. Our GeneTrove division continues to generate near-term revenue while enhancing our own antisense drug discovery efforts and our patent portfolio.

In our Ibis division we have developed technology that has the potential to revolutionize the detection and treatment of infectious disease. We are creating a sensor that can detect known and unknown infectious agents, and are working to discover small molecule drugs that work by binding to RNA. Our scientists have invented methods of identifying common binding sites in RNA that facilitate the identification of organisms or serve as targets for drug binding. We have also invented mass spectrometry-based screening methods for both diagnostic and drug discovery applications. In a program called Triangulation Identification

Genetic Evaluation of biological Risks, or TIGER, we are applying our Ibis technology to develop a sensor to detect infectious agents that could be used in biological warfare. We are collaborating with San Diego-based Science Applications International Corporation, or SAIC, on this multi-year program funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $9.8 million for its efforts related to TIGER. Since the division's inception, Ibis has received significant financial support from various government agencies to use its technology to develop broad-spectrum anti-infective drugs that we believe will have usefulness in national defense. In early 2002, Ibis received a three-year contract to continue its drug discovery program with the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. The contract provides for funding of up to $2.4 million.

In addition to the projects with government agencies, Ibis collaborated with Pfizer from June 2000 through June 2002 for the discovery and development of small molecule drugs against certain RNA targets. During this period, Ibis earned two research milestones totaling $4.0 million. This collaboration ended in June 2002 in accordance with its terms.

We have a broad patent portfolio covering our technologies. We have rights to nearly 1,200 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. The principal purpose of our intellectual property portfolio is to protect our 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, which includes licensing. Licensing partnerships may include antisense drug discovery alliances such as those we have with Lilly and Amgen, as well as GeneTrove functional genomics collaborations like those we have with Amgen, Chiron and Pharmacia. Licensing partnerships may also include Ibis drug discovery alliances like the one we had with Pfizer.

In addition, we have issued licenses to our functional genomics patents, like our licenses to Chiron, Amgen, Sequitur and atugen AG, as well as licenses to our non-antisense patents, like our license to Eyetech Pharmaceuticals, Inc. In 2002, we successfully defended our patent estate when we settled a patent infringement lawsuit against Sequitur on terms favorable to us.

Drug Discovery and Development

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 the detection and treatment of infectious diseases.

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. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense technology is different from traditional drug discovery because it specifically targets disease-causing proteins before the body produces them. We design our antisense drugs, or antisense inhibitors, to act earlier in the disease process than traditional drugs and to interrupt the production of disease causing proteins without disrupting proteins responsible for the body's normal functioning.

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

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

We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides, which resemble DNA and RNA 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 because antisense drugs interact selectively with the specific RNA and not with the closely related members of the group. It is easier to differentiate between closely related proteins at the RNA sequence level than by binding to the protein itself, as traditional drugs do. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique specificity means that antisense drugs may be 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 requires companies to identify a small molecule that will interact with protein structures to affect the disease-causing process. Since predicting which small molecules will do this has proven to be difficult, traditional drug discovery involves testing hundreds of thousands of small molecules for their ability to interfere with protein function. As a result, traditional drug discovery is a labor intensive, low probability endeavor. On the other hand, we design our antisense compounds to bind to mRNA structures through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the mRNA receptor.

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, like oral, topical cream, subcutaneous, intravitreal, aerosol and enema, of antisense drugs that further expand the potential for antisense technology.

GeneTrove Target Validation and Gene Functionalization

In our functional genomics division, GeneTrove, we use antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. This information forms the basis of the first step of our antisense drug discovery program. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners, Lilly and Amgen.

Due to its specificity, versatility and efficiency, antisense is an important technology platform for conducting biological studies to identify what a gene does, called gene functionalization, and to determine whether a specific gene is a good target for drug discovery, called target validation. We produce optimized, target-specific antisense inhibitors to genes based on a variety of specialized technologies that we have created and/or integrated, including a proprietary automated rapid throughput screening process.

Through our streamlined process, we can produce antisense inhibitors to a particular gene for use in cell culture studies in a matter of days. Scientists can use these 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. We have created inhibitors to thousands of genes, validated many targets and dissected numerous disease pathways. Additionally, we have created libraries of antisense inhibitors to identify novel gene function.

We have commercialized this first step in our antisense drug discovery program through our GeneTrove division by providing valuable gene functionalization and target validation services to pharmaceutical and biotechnology companies. Our collaborators use the information we generate to enhance and expedite their drug discovery decisions. Our GeneTrove collaborations generate near-term revenue for us, and broaden the industry's exposure to antisense technology.

Our business strategy for GeneTrove involves three components. The first is the use of antisense-based functional genomics to facilitate the discovery and development of antisense drugs for ourselves and for our partners. Second, we offer custom target validation collaborations to partners, in which research is focused on identifying the role and value of specific genes as drug targets for their own drug discovery programs. Current collaborators include Abbott, Amgen, Celera Genomics, Chiron, GlaxoSmithKline, Johnson & Johnson, Lilly and Merck. The third component, functional genomics

intellectual property licensing, encourages industry partners to work with GeneTrove for antisense-based gene functionalizaton and target validation. Partners may access our intellectual property as part of a target validation collaboration, as in the case of Amgen, Chiron and Pharmacia. Companies may choose to license our technology to support their use of antisense, independent of a collaboration with us. Sequitur, Pfizer and atugen AG, are examples of such licensees. In August 2001, we added a subscription database product to GeneTrove's offerings. However, we were unsuccessful in generating subscription customers for our database product. In November 2002 we announced the termination of the database offering, and the reorganization of the GeneTrove division. The restructuring plan resulted in a reduction in our workforce of approximately 25 people and also provided for the write-down of certain intellectual property.

Our GeneTrove division enhances our own antisense drug discovery efforts and our patent portfolio through custom target validation collaborations and intellectual property licenses while generating near-term revenue for us.

Ibis Technology Platform

In our Ibis division we have developed technology that has the potential to revolutionize the detection and treatment of infectious disease. Our Ibis technology uses our success in RNA-targeted drug discovery and development and expands on our ability to convert genomics data into information for diagnostics and drug discovery.

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, including those derived from natural products, using novel mass spectrometry approaches.

Based on this expertise, we are developing a diagnostic instrument to detect infectious agents that may be used in biological attacks, and we are working to discover drugs that work by binding to RNA targets.

In the area of diagnostics, Ibis is applying its core technology to a DARPA-sponsored research program called TIGER. In the TIGER program we are developing a sensor to detect infectious organisms, including known, unknown, unculturable or bioengineered agents that could be used in biological attacks. We received our initial TIGER funding from DARPA in October 2001. The TIGER contract builds on the biological warfare countermeasure research Ibis 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 is working with SAIC on TIGER. 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 original TIGER contract included funding of up to $8.9 million. During 2002, DARPA increased the contract amount to $9.8 million.

Ibis' therapeutic focus is the discovery of novel, potentially orally bioavailable, low molecular weight, or small molecule, drugs to treat infectious disease and cancer. Since its inception, Ibis has received significant financial support from government-funded grants and contracts to use its technology to assist in national defense. In March 2002, Ibis transitioned its government-sponsored

research program to discover novel broad-spectrum antibacterial drugs for biological warfare defense to USAMRIID. Ibis received a three-year contract from USAMRIID to advance its work in this area and expects to receive funding of up to $2.4 million under this contract.

Ibis also has research relationships with several other government entities including the United States Navy, the Federal Bureau of Investigations and the Center for Disease Control and Prevention.

In addition to the projects with government agencies, Ibis collaborated with Pfizer from June 2000 through June 2002 to discover and develop small molecule drugs against certain RNA targets. During this period, Ibis earned two research milestones totaling $4.0 million. This collaboration ended in June 2002 in accordance with its terms.

Product Approved and Products Under Development

We have successfully developed the first antisense drug to reach the market, Vitravene, for CMV retinitis. Our commercialization partner, Novartis Ophthalmics AG, markets this drug.

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

Products Approved and in Development

Product(1)	Target	Potential Disease Indication(s)	Development Status(2)	Commercial Rights
Vitravene (I)	Antiviral	CMV Retinitis	Commercially available in the U.S., Europe, Australia and Brazil.	Isis/Novartis Ophthalmics(3)
Affinitak (formerly LY900003 or ISIS 3521) (P)	PKC-alpha	Cancer—Non-Small Cell Lung Cancer, Others	Phase III	Lilly
Alicaforsen (ISIS 2302) (P)	ICAM-1	Crohn's Disease	Phase III	Isis
Alicaforsen (ISIS 2302) (E)	ICAM-1	Ulcerative Colitis, Pouchitis	Phase II	Isis
ISIS 14803 (P)	Antiviral	Hepatitis C	Phase II	Isis
ISIS 2503 (P)	H-ras	Cancer—Pancreatic, Others	Phase II	Isis
ISIS 104838 (P,O)*	TNF-alpha	Rheumatoid Arthritis	Phase II	Isis
ISIS 104838 (T)*	TNF-alpha	Psoriasis	Phase II	Isis
OGX-011 (P)*	Clusterin	Cancer—Prostate, Others	Phase I	Isis/OncoGenex
ISIS 23722 (P)*	Survivin	Cancer	Preclinical	Lilly
ISIS 113715 (P)*	PTP-1B	Diabetes	Preclinical	Isis
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

(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 worldwide rights to distribute Vitravene.

* Second-generation drugs

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. The most recent statistics available from the Centers for Disease Control indicate there are more than 362,000 active AIDS cases in the United States. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have 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 that we discovered and developed. Novartis Ophthalmics AG, the eye health unit of life sciences leader, Novartis AG, and our worldwide distribution partner for this drug, launched Vitravene in November 1998. For a more detailed discussion of this collaboration, see "Collaborative Arrangements and Licensing Agreements—Novartis Ophthalmics." Vitravene is commercially available in the U.S., Europe, Australia and Brazil.

Cancer

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

Affinitak—Affinitak, which we licensed to Lilly in August 2001, is our antisense compound in Phase III clinical development for non-small cell lung cancer. Affinitak inhibits the production of one particular isotype, the alpha isotype, of protein kinase C, or PKC. PKC alpha is a member of a family of proteins that are associated with both normal and abnormal cell growth. PKC alpha has been shown to be involved in cancer cell growth and maintenance. In preclinical studies, 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 all the different PKC isotypes.

We recently announced the results of our Phase III clinical trial of Affinitak in combination with traditional cancer chemotherapy drugs to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in a primary log-rank analysis of overall survival, the primary endpoint of the trial, of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone. The median survival for the Affinitak treated patients was ten months compared to 9.7 months for those patients treated with the chemotherapy alone.

It is common in clinical trials to perform additional analyses of the data using other standard statistical methods or tests, and after conducting other analyses of the trial, we observed evidence of activity of Affinitak in this trial. For example, our statistical analysis plan allowed for a stratified log-rank analysis of survival of all 616 patients in the trial. The benefit of the stratified log-rank analysis is that it considers a number of predefined variables, including duration of treatment. We observed that survival of the Affinitak treated patients was greater than that of the patients who received the

chemotherapy alone. This result was statistically significant. Another potentially important observation from the trial is that those patients who completed the prescribed course of therapy, 6 cycles, experienced a survival benefit compared to those patients who did not complete therapy. A survival analysis of the 256 patients who completed the prescribed 6 cycles of the chemotherapy showed a median survival of 17.3 months for Affinitak patitents compared to 14.4 months for patients who received the chemotherapy alone. This result suggests that the duration of treatment with Affinitak may contribute to improved survival. Additionally, in those patients who completed the prescribed course of therapy, results favored the Affinitak group across multiple secondary endpoints, including time to disease progression, time to treatment failure and duration of remission.

The addition of Affinitak to carboplatin and paclitaxel was well tolerated. There were no increases in severe toxicities or toxicity related deaths in patients receiving Affinitak, compared to those receiving the chemotherapy alone. The most common side effects among patients in the study were fatigue and nausea. Patients in the study receiving Affinitak in combination with the chemotherapy had a higher rate of moderate thrombocytopenia, nausea and vomiting. Further, because Affinitak is given via continuous intravenous infusion, Affinitak treated patients had a higher incidence of catheter-related infections.

All of the above results are based on our initial assessment of the data. We and Lilly are performing an in-depth analysis of the data and we expect to submit the complete findings of the trial for scientific presentation at an appropriate medical meeting later this year. Lilly plans to evaluate Affinitak's performance in Lilly's on-going Phase III trial, in which patients being treated with Affinitak in combination with gemcitabine and cisplatin. As we proceed with these evaluations, Lilly and we will make a decision about the further development of Affinitak.

According to the American Cancer Society, lung cancer is the leading cause of cancer death for both men and women. In 2003, an estimated 171,000 new cases of lung cancer are expected to be diagnosed and approximately 157,000 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 80 percent of lung cancer diagnoses in the United States.

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 supported continued development of ISIS 2503 in Phase II trials for the treatment of pancreatic, breast and non-small cell lung cancer. We have recently completed a Phase II study of ISIS 2503 in pancreatic cancer. Final results of this Phase II study demonstrated that 57.5 percent of 48 patients who received ISIS 2503 plus gemcitabine survived six months or longer. Gemcitabine is the standard care for pancreatic cancer. Based on these results reported in December 2002, we are considering various strategies, including partnering, for the further development of this compound in pancreatic cancer.

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, like 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. When combined with other cancer treatments in preclinical model systems, OGX-011 has been shown to significantly improve tumor reduction and delay disease progression in prostate, lung, bladder and renal cancer. These findings support the continued development of OGX-011 in combination with standard chemotherapy and other agents.

OncoGenex initiated a Phase I program of OGX-011 in patients with prostate cancer in December 2002. This Phase I trial is evaluating OGX-011 in combination with hormone therapy prior to surgical removal of the prostate. A second Phase I study is scheduled to start in 2003 and will evaluate OGX-011 in

combination with TAXOTERE® in various solid tumors. OGX-011 is our third anti-cancer drug in human clinical trials, and the first second generation antisense anti-cancer drug.

ISIS 23722—We licensed our preclinical anti-cancer candidate, ISIS 23722, to Lilly in 2002, as part of the expansion of our Lilly research collaboration into cancer. The compound targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin is one of the most abundantly expressed proteins in cancers. Our researchers and collaborators have shown that inhibiting expression of survivin by ISIS 23722 in cancer cells inhibits the growth of cancer cells and kills cancer cells. Since survivin is not expressed in normal cells in the body, we expect that this drug will have fewer side effects than traditional chemotherapy.

Inflammatory Diseases

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

Alicaforsen (ISIS 2302)—The most advanced compound in our cell adhesion program selectively inhibits ICAM-1 gene expression. 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. We are currently evaluating alicaforsen in two Phase III studies for the treatment of Crohn's disease. Additionally, we are conducting Phase II studies of alicaforsen enema formulation for the treatment of ulcerative colitis and pouchitis.

- ***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. According to the Crohn's and Colitis Foundation of America, up to one million people have inflammatory bowel disease, with occurrences evenly split between Crohn's disease and Ulcerative Colitis, or UC. According to the European Federation of Crohn's and Ulcerative Colitis Associations a similar number of people in Europe are affected. Two Phase III trials of alicaforsen in people with active Crohn's disease are in progress. One is enrolling patients in North America and the other in Europe. These studies are evaluating the safety and efficacy of alicaforsen. We expect to complete the enrollment of approximately 300 patients in total for both studies by early 2004.

  In October 2002, we reported results of an open-label Phase II clinical trial in patients with Crohn's disease showing that the antisense drug may produce clinical disease remissions. In late 1999, we completed a 300 patient pivotal trial of alicaforsen in Crohn's disease, which we

  initiated based on positive results from an earlier Phase II trial. The initial analysis of the data from the 300 patient trial did not show efficacy and the data did not support an NDA filing. However, further analysis of the data indicated that those patients who received higher exposure to alicaforsen were more likely to experience complete clinical remission of their disease, which was the primary endpoint of the pivotal trial. The current Phase III trials are in response to this additional analysis and patients are receiving higher doses of alicaforsen than previously studied in controlled trials.

- ***Ulcerative Colitis***—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 typically include diarrhea, rectal bleeding and abdominal pain. UC differs from Crohn's disease, as it affects only the colon. According to the Crohn's and Colitis Foundation of America up to one million people have inflammatory bowel disease, evenly split between Crohn's disease and UC. According to the European Federation of Crohn's and Ulcerative Colitis Associations a similar number of people in Europe are affected.

  In October 2001, we reported that data from a Phase II clinical trial demonstrated that alicaforsen improved symptoms of patients with UC. Patients receiving an enema formulation of alicaforsen experienced a dose-dependent reduction in disease activity index score, or DAI, and clinical activity index score, or CAI. Further, many of these patients did not require additional medical and surgical intervention during the six month study period. The DAI and CAI measure the signs and symptoms that patients with ulcerative colitis typically experience. No serious side effects were observed in patients in this Phase II trial. Based on these favorable results, in November 2002 we launched a multi-center Phase II trial in the U.S. We designed the 170-patient U.S. study to compare the safety and efficacy of an enema formulation of alicaforsen to mesalamine enema, a widely used medication for ulcerative colitis. We expect to complete enrollment in this trial in early 2004. In the second half of 2003, we expect to begin an additional, multi-center Phase II trial to compare dose and schedule regimens.

- ***Pouchitis***—Pouchitis is an inflammation of the ileo-anal pouch and is a common complication in ulcerative colitis patients requiring surgical removal of the diseased colon. Pouchitis is a disorder without satisfactory medical therapy. Symptoms include an increased number of stools, rectal bleeding, abdominal cramping and fever. We are conducting a Phase II trial of an enema formulation of alicaforsen for the treatment of patients with pouchitis. We plan to report data from this trial in the first half of 2003.

- ***Psoriasis***—In February 2002, we reported results of a Phase II clinical trial in which a topical cream formulation of alicaforsen demonstrated improvement in patients with mild to moderate plaque psoriasis. There were no significant side effects observed in the trial. Although we observed evidence of activity in this disease, we have decided to focus our resources and efforts on the rest of our development projects, so we are discontinuing clinical development of topical alicaforsen for psoriasis.

ISIS 104838—ISIS 104838 is a second-generation antisense inhibitor of TNF-alpha and the 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 and psoriasis. TNF-alpha is involved in bone and cartilage absorption, facilitates inflammation and inhibits bone formation. Most patients with rheumatoid arthritis have high levels of TNF-alpha.

- ***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 causing 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 our first Phase II trial of ISIS 104838 in patients with rheumatoid arthritis we are studying the ability of different concentration of ISIS 104838 to reduce TNF-alpha levels in blood and synovial tissue. In our second Phase II trial of ISIS 104838 in rheumatoid arthritis we are evaluating the safety and efficacy of ISIS 104838. This 3-month dose ranging trial will evaluate various doses of ISIS 104838 versus a placebo. The drug is administered by subcutaneous injection. We plan to report results from both of these trials in late 2003. As we reported earlier in 2001, Phase I trials of intravenous infusion and subcutaneous injection of ISIS 104838 demonstrated the potential for a more convenient dosing schedule of once every 2 to 4 weeks as well as safety advantages over first-generation antisense drugs. The subcutaneous study demonstrated substantial improvement in local tolerability over first-generation antisense drugs. The development of an oral formulation of ISIS 104838 had been the focus of our Orasense joint venture with Elan. At the end of 2002, Elan concluded its participation in the Orasense collaboration, in conjunction with their continuing restructuring efforts. As a result, we have regained all rights to ISIS 104838, with a potential nominal royalty due to Orasense. We are continuing to advance the development of oral formulation platform technology.

- ***Psoriasis***—According to the National Psoriasis Foundation, more than 7 million people in the United States have psoriasis. Psoriasis is a non-contagious disorder of the skin characterized by abnormal growth or overproduction of skin cells. The most common type is plaque psoriasis, which accounts for 80% of psoriasis diagnosis. We are completing a Phase II clinical trial of a topical formulation of ISIS 104838 in patients with psoriasis. We plan to report data from this trial in 2003. Based upon the study results, we will determine the development plan for ISIS 104838 for the treatment of psoriasis.

ISIS 107248—ISIS 107248, or ATL 1102, is a second-generation antisense inhibitor of CD49d, which is a subunit of VLA-4. 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. In December 2001, we licensed ISIS 107248 to Antisense Therapeutics Limited, or ATL. Under our agreement with ATL, we were responsible for completing the required preclinical studies for ISIS 107248 and for manufacturing the bulk drug for human clinical trials at ATL's expense. ATL is responsible for the future clinical development and the commercialization of the drug. ATL expects to initiate a Phase I clinical trial of ISIS 107248 for the treatment of multiple sclerosis in the first half of 2003.

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 have been infected with HCV and 10,000 to 12,000 people in the United States are expected to die from his disease each year. Physician's attempt to eradicate this virus from chronically infected individuals by using Interferon-alpha therapy, either alone or in combination with the drug ribavirin. Patients with genotype 1 HCV have less than a 50% chance of having a sustained response with the current standard of care, pegylated 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 November 2002, Isis presented data from two studies that showed ISIS 14803 is active in drug resistant, genotype 1 HCV patients, the most difficult-to-treat segment of the HCV patient population. In a 12 week Phase II study, the drug demonstrated promising antiviral activity by producing up to 3.8 log reductions in the level of virus in the blood, or viral titers, a 6,300-fold decrease in the viral loads of patients with this disease. This study is ongoing and we plan to report final results in 2003. In a four-week 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 the level of virus in the 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. Flu-like symptoms, headache and fatigue were the most common side effects observed in the trials. In 2003 we plan to evaluate ISIS 14803 in combination with currently used HCV treatments in an additional Phase II study.

The development of ISIS 14803 had been the focus of our joint venture with Elan, HepaSense. In late 2002, Elan concluded its participation in the HepaSense collaboration, in conjunction with their continuing restructuring efforts. As a result, we have regained all rights to ISIS 14803, with a potential nominal royalty due to HepaSense.

Metabolic Diseases

We are pursing the discovery and development of antisense drugs for metabolic diseases such as diabetes and obesity. These chronic diseases affect millions of people and represent significant areas of unmet medical need. We believe that our second-generation antisense drugs will have properties that will make them attractive therapies

ISIS 113715—ISIS 113715 is our second-generation antisense inhibitor of the PTP-1B gene for Type 2 diabetes. According to the American Diabetes Association, diabetes affects nearly 17 million people and Type 2 diabetes constitutes 90 percent of those cases. An antisense inhibitor of PTP-1B represents a new approach to the treatment of diabetes. 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.

The preclinical studies of ISIS 113715 demonstrate compelling activity in multiple diabetic animal models and suggest activity as an insulin sensitizer without causing hypoglycemia and while reducing cholesterol and weight gain. In December 2002 we regained the full product rights to ISIS 113715 from Merck. We plan to initiate Phase I clinical trials of ISIS 113715 for the treatment of Type 2 diabetes this year.

ISIS 13650—ISIS 13650 is an inhibitor of c-*raf* kinase for the treatment of diabetic retinopathy and age-related macular degeneration. Diabetic retinopathy is an ocular complication of diabetes. The incidence of these conditions continues to grow with the advancing age of the U.S. population. In preclinical studies,

antisense inhibition of c-raf kinase is associated with a reduction of neovascularizatio, or growth of blood vessels, which can obstruct vision. ISIS 13650, a second-generation antisense product, is in preclinical development. We are exploring options for its further development.

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 discovering anti-infective drugs and creating mass spectrometry-based technology for infectious disease 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 like 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.

2002 Business Development Highlights

We are focused on establishing new partnerships and on advancing and building upon existing relationships. We currently have agreements with more than a dozen partners. These span all four areas of our business: antisense drug discovery and development, GeneTrove, Ibis and our intellectual property estate. The following is a list of our business development highlights for 2002:

- Expanded our Lilly drug discovery collaboration to include selected targets in cancer.
- Expanded our Lilly antisense alliance to include a new Affinitak manufacturing agreement.
- Initiated four new GeneTrove collaborations with GlaxoSmithKline, Merck, Amgen and Pharmacia.
- Achieved a milestone payment for the progress in our Amgen antisense drug discovery collaboration.
- Reacquired the rights from Orasense, a joint venture with Elan, to the oral formulation of ISIS 104838, our antisense inhibitor of TNF-alpha for rheumatoid arthritis.
- Reacquired the rights from HepaSense, a joint venture with Elan, to ISIS 14803, our antisense drug to treat hepatitis C virus.
- Extended our Hepatitis C drug discovery collaboration with Merck for a second time.

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 Affinitak, our antisense drug which is being tested in a Phase III trial 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. In 2002, Lilly and we expanded this collaboration to include oncology and the license of ISIS 23722, our antisense inhibitor of survivin.

- 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. We can repay this loan at our option in either cash or our common stock, at a fixed conversion price of $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 upfront license fee for Affinitak, the amount Lilly has committed to pay us for the remaining development and registration costs for Affinitak and the $100 million Lilly has committed to loan us. Assuming success of Affinitak 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.

In September 2002, we further expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we upgraded and expanded our manufacturing facility. We added a new state-of-the-art manufacturing suite dedicated to Affinitak. Lilly

provided us with funding in the form of a loan of up to $21 million, to build the Affinitak suite. We will repay the loan from Affinitak success milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan. In February 2003, we completed construction of the facility, which is located on our Carlsbad campus in an existing building.

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. In August 2002 and February 2003, we earned progress-related research milestones under this drug discovery collaboration.

Merck & Co., Inc.

In April 2002, we extended for a second time a research collaboration, with Merck 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 may 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, research and clinical development milestone payments, and royalties upon commercialization of drugs that arise from the collaboration. In October 2001 and April 2002, we earned milestone payments for progress in the collaboration. We began the original three year drug discovery collaboration with Merck in June 1998 and announced the first one year extension in May 2001. We expect the collaboration will end in May 2003 in accordance with its terms.

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. We have implemented this integral component of our

strategy through our partnerships with major pharmaceutical companies and with Antisense Therapeutics Limited, OncoGenex and Pantheco. Our partnerships with OncoGenex, ATL and Pantheco represent our ability to broaden the reach of antisense technology in emerging companies globally. We believe we will have more of these 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

ISIS 107248 has been demonstrated to have positive effects in animal models for the treatment of certain inflammatory diseases such as multiple sclerosis. In December 2001, we licensed ISIS 107248 to Antisense Therapeutics Limited, an Australian company publicly traded on the Australian Stock Exchange. We were responsible 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. ATL expects to initiate a Phase I clinical trial of ISIS 107248 for the treatment of multiple sclerosis in the first half of 2003. In addition, we are participating 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 we provide them 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. In December 2002, ATL successfully completed a subsequent share placement in which we participated as an investor. We currently own approximately 15% of ATL's equity and hold options for additional shares. If all ATL's options were exercised, including ours, our ownership would remain at approximately 15%.

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. We conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. We also manufactured OGX-011 for preclinical and Phase I/II studies. OncoGenex has responsibility to perform Phase I clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and to perform Phase I/II clinical trials in combination with standard chemotherapy in patients with solid tumors known to express clusterin including lung, prostate, renal, bladder and ovarian cancers. In December 2002, OncoGenex and we announced the initiation of a Phase I clinical trial of OGX-011 in patients with prostate cancer. OncoGenex plans to start a second Phase I trial in 2003.

Pantheco

As part of a licensing agreement for our novel antisense chemistry Peptide Nucleic Acid, PNA, completed in November 1998, we received common shares in Pantheco. In September 2000, we entered into a second license for PNA with Pantheco, whereby we received additional common shares upon the completion of Pantheco's October 2000 financing. As a result of Pantheco's October 2000 financing, our total ownership in Pantheco was 22% and valued at approximately $1.1 million. In 2001, Pantheco issued additional shares and Isis' holdings in Pantheco declined to 15.5% and we currently hold 15.5% of Pantheco's outstanding shares.

Merck & Co., Inc.

In May 2001, we licensed to Merck our preclinical antisense drug candidate, ISIS 113715. In December 2002, we reacquired full product rights to ISIS 113715. ISIS 113715 is currently in preclinical development for adult onset, or Type 2, diabetes. We expect to initiate Phase I trials of ISIS 113715 in 2003.

Elan—HepaSense—Hepatitis C

In January 2000, we formed a joint venture with Elan, called HepaSense, to develop our antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus or HCV. As part of the original joint venture, both Elan and we licensed significant technology to HepaSense. Through the HepaSense joint venture we were able to advance the development of ISIS 14803, including:

- completing an initial Phase I/II clinical trial that demonstrated acceptable safety and reduction of HCV viral titer, or levels of virus in blood, for which we received a development milestone from Elan; and

- initiating a Phase II clinical trial of ISIS 14803 in patients with chronic Hepatitis C infections. Results from this ongoing Phase II clinical trial demonstrated that ISIS 14803 produces significant reductions of viral levels in the blood of patients with drug resistant Hepatitis C.

In November 2002, Elan concluded its participation in the HepaSense collaboration in conjunction with its continuing restructuring efforts. As a result, we have regained all rights to ISIS 14803, with a potential nominal royalty due to HepaSense. HepaSense will distribute the royalty to Elan and us on a pro rata basis based on each parties' equity ownership in HepaSense. This favorable outcome allows us to pursue the clinical development of ISIS 14803.

Under the terms of the HepaSense joint venture, we provided 80.1% of the funding necessary to operate the joint venture while Elan provided 19.9%. In connection with this funding arangement, Elan made available to us a $12.0 million line of credit evidenced by a convertible promissory note, $7.2 million of which we used to provide funding to HepaSense. In July 2002, we prepaid the $7.9 million in outstanding principal and accrued interest on the HepaSense convertible promissory note held by Elan. As of December 31, 2002, the HepaSense convertible promissory note was fully paid and we cannot borrow any additional funds against it.

As part of the joint venture, Elan purchased $7.5 million of our common stock at a premium to its market price and we issued Elan warrants, which have a five year life and expire in January 2005. Elan also purchased our Series B preferred stock, which is convertible in the future into either our stock or stock in HepaSense. In April 2002, we achieved a development milestone in the HepaSense collaboration, triggering a $3.8 million equity purchase by Elan of our common stock at a premium to its market price. As part of the milestone investment, Elan also received warrants to purchase shares of our common stock, which have a five year life and expire in April 2007.

Elan—Orasense—Oral Formulation

In April 1999, we formed a joint venture, called Orasense, with Elan to develop a platform technology for the oral delivery of antisense drugs. As part of the agreement, we licensed to Orasense the oral rights to ISIS 104838, our antisense inhibitor for TNF-alpha. Through the Orasense joint venture, we were able to share some of our development expenses for ISIS 104838 with Elan and were able to significantly advance our oral delivery technology. For example, Orasense completed a Phase I clinical trial of ISIS 104838 of oral solid formulations to evaluate the absorption, distribution, metabolism and elimination of ISIS 104838 in oral dosage forms. The results from this study demonstrated that antisense drugs can be administered orally and support further clinical development of oral antisense drugs.

In 2002, Elan and we agreed to extend the Orasense collaboration. Effective December 31, 2002 Elan concluded its participation in the Orasense collaboration in conjunction with its continuing restructuring efforts. As a result, we have regained all rights to ISIS 104838, with a potential royalty due to Orasense. Orasense will distribute the royalty to Elan based on Elan's equity ownership in Orasense. This favorable outcome allows us to pursue further clinical development of ISIS 104838 and oral antisense drugs.

Under the terms of the Orasense joint venture, we provided 80.1% of the funding necessary to operate the joint venture while Elan provided 19.9%. In connection with this funding arangement, Elan made available to us an $18.4 million line of credit evidenced by a convertible promissory note, $15.5 million of which we used to provide funding to Orasense. In July 2002, we prepaid $11.8 million in outstanding principal and accrued interest on the Orasense convertible promissory note held by Elan. Approximately $5.1 million in principal remains outstanding under the Orasense convertible promissory note as of December 31, 2002. We cannot borrow any additional principal under the Orasense convertible promissory note. However, interest will continue to accrue on the outstanding amounts. The maturity date for the Orasense convertible promissory note is April 19, 2005.

As part of the joint venture, 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 our Series A preferred stock. Elan also received warrants which have a five year life and expire in April 2004. In August 2002, the holder of our Series A preferred stock exercised its option to convert the Series A shares and related cumulative dividends on the Series A preferred stock into Isis common stock. The transaction converted all the outstanding shares of our Series A preferred stock into shares of our common stock.

Antisense Commercialization

Novartis Ophthalmics AG

In 1997, we entered into an agreement with Novartis Ophthalmics AG, formerly CIBA Vision Corporation, granting them exclusive worldwide distribution rights for Vitravene, an antisense compound that we discovered and developed. The terms of the agreement provided for us to receive $20 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. In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Vitravene is commerically available in the U.S., Europe, Australia and Brazil. Novartis Ophthalmics AG, the eye health unit of life sciences leader, Novartis AG, and our worldwide distribution partner for this drug, launched Vitravene in November 1998. While Novartis Ophthalmics AG markets and sells Vitravene worldwide, we manufacture and sell Vitravene to Novartis Ophthalmics AG at a price that allows us to share the commercial value of the product with them.

GeneTrove Collaborations

Our GeneTrove division has partnerships with major pharmaceutical and biotechnology companies in which we provide one or more of the following services:

- Gene functionalization and/or target validation services to help our partners validate and prioritize genes for their drug discovery programs,
- access to our inhibitor library,
- a license to specific intellectual property that a partner may use in its in-house functional genomics programs and/or for its customers

Our partners in 2002 included:

- Abbott Laboratories
- Amgen
- atugen AG
- Aventis
- Celera
- Chiron Corporation
- GlaxoSmithKline plc.
- Johnson & Johnson Pharmaceutical Research & Development, LLC.
- Merck
- Pfizer
- Pharmacia Corporation

We recently extended GeneTrove's collaboration with Celera to end in June 2003. GeneTrove's collaborations with Abbott and Aventis concluded in 2002 under the terms of their agreements.

Ibis Collaborations

Our Ibis Therapeutics division has entered into numerous contracts and grants with various government agencies to complete research and development work for defense against biological warfare attacks and threat scenarios. The contracts and grants include a multi-year contract, with expected funding up to $9.8 million, with the Defense Advanced Research Projects Agency, or DARPA, a three-year contract, with expected funding up to $2.4 million, with the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, and a one-year grant from the Federal Bureau of Investigation, or FBI.

In addition to the projects with government agencies, our Ibis Therapeutics division entered into a collaboration with Pfizer in June 2000 for the discovery and development of small molecule drugs against certain RNA targets. This collaboration ended in June 2002 in accordance with its terms.

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 this long-term supply agreement, 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 us for our in-house drug discovery efforts and to major pharmaceutical and biotechnology customers. We paid IDT $5 million toward our future purchase of antisense inhibitors. As of December 31, 2002, the balance of our prepayment is $4.5 million.

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 that 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 have paid IDT $3.9 million to date and will pay IDT $1.1 million over the next three 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 agreed to pay us $6.0 million in Hybridon common stock before May 2004. In September 2001 and October 2001, we issued to Hybridon 357,143 shares of our common stock valued at $5.0 million and 500,000 shares of our common stock valued at $10.0 million, respectively. In May 2002, Hybridon issued to us 1,005,499 shares of its common stock valued at $1.3 million and paid us $700,000 in cash. In August 2002, we and Hybridon cancelled the remaining reciprocal financial obligations related to this agreement. Specifically, Hybridon owed us an additional $4 million worth of Hybridon common stock, payable immediately. We owed Hybridon $4.5 million in cash or stock, due in May 2003. The cancellation of the obligations resulted in a decrease to our carrying value for the license in the amount of $500,000.

Molecular Biosystems, Inc.

In March 2001, we amended a non-exclusive Patent License Agreement, which we entered into with Molecular Biosystems, Inc. in September 1992. The amendment 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 Macugen, formerly EYE001, a non-antisense compound intended for use in the treatment of ophthalmic diseases. Macugen is currently in Phase II/III clinical trials sponsored by Eyetech. 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 licensed some of our novel chemistry patents to Roche, a business unit of Roche Diagnostics, for use in the production of Roche's diagnostic products. The royalty-bearing license grants Roche non-exclusive worldwide access to some of our proprietary chemistries, in exchange for initial and ongoing payments from Roche to us.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides, like those we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide compounds, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide compounds. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the compounds. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

In September 2002, we further expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we expanded our manufacturing facility. We upgraded our existing manufacturing suite that is dedicated to the production of products for us and our non-Lilly partners. In addition, we added a second state-of-the-art manufacturing suite dedicated to Affinitak. Lilly provided us with funding in the form of a loan of up to $21 million, to build the Affinitak suite. We will repay the loan from Affinitak success milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan. In February 2003, we completed construction of the facility, which is located on our Carlsbad campus in an existing building.

In addition, we have contractual obligations to manufacture clinical trial materials and/or commercial supply for Amgen, ATL, Lilly, Novartis and OncoGenex. We believe we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs as well as meet our current internal research and clinical needs. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale, 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, 2003, we own or have exclusively licensed nearly 1,200 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 and other antisense inhibitors, in gene functionalization and target validation, including chemistries, antisense inhibitor designs called "motifs", methods of use of antisense inhibitors and mechanisms of action by which antisense inhibitors inactivate an RNA target;

- Composition of matter claims to core chemistries for oligonucleotides, which cover our rights to the building blocks of our compounds;

- Composition of matter claims to antisense compounds targeted to particular RNA target sequences, which cover our drugs;

- Use claims for using oligonucleotides targeted to particular disease targets, which cover our right to use oligonucleotide-based drugs to treat specific diseases or 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;

- Method claims for identifying unknown bioagents utilizing mass-spectrometry-based analyses; and

- Methods claims for rapidly discovering antisense oligomeric compounds, which cover our rapid throughput method of discovering antisense oligonucleotides.

On July 9, 2001, we commenced an action against Sequitur, Inc. in the United States District Court for the Southern District of California, No. 01 CV 1223 BTM (JFS), for infringement of U.S. Patent No. 6,001,653. We settled this action and two subsequent actions we commenced against Sequitur on terms favorable to us. On September 13, 2002 the court dismissed with prejudice all three actions.

Government Regulation

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

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

In addition to regulations enforced by the FDA, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

Competition

For many of their applications, antisense-based drugs as well as Ibis small molecules will compete 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 this technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies.

Vitravene and our other products under development address numerous markets. The diseases targeted by our drugs for which we may receive regulatory approval will determine our competition. For certain of our products, an important factor in competition may be the timing of market

introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market is an important competitive factor. We expect that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price and patent position.

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, that were introduced prior to Vitravene's approval, have prolonged survival in HIV-infected individuals. This resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections including CMV retinitis.

We currently have two drugs in Phase III trials. We licensed Affinitak, 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 Affinitak. If future studies support commercialization, we expect that physicians would use Affinitak 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 alicaforsen, which we are studying in patients with Crohn's disease. Alicaforsen will likely compete with Johnson & Johnson's drug, Remicade, which is approved for the treatment of Crohn's disease and rheumatoid arthritis.

Employees

As of February 28, 2003 we employed 523 individuals, of whom 159 hold advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with its employees to be good.

Executive Officers

The following set forth certain information regarding our executive officers as of February 28, 2003:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	57	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, Esq.	47	Director, Executive Vice President, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.	46	Vice President, Antisense Research
Richard K. Brown, Ph.D.	50	Isis Vice President and President, GeneTrove
Douglas L. Cole, Ph.D.	55	Vice President, Development Chemistry and Pharmaceutics
David J. Ecker, Ph.D.	48	Isis Vice President and President, Ibis Therapeutics
Arthur A. Levin, Ph.D.	49	Vice President, Development
Patricia Lowenstam	56	Vice President, Human Resources and Operations
Karen Lundstedt	38	Vice President, Corporate Communications
John McNeil	38	Vice President, Informatics
Aron Stein, Ph.D.	44	Vice President, Regulatory Affairs and Quality Assurance

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

Dr. Crooke was a founder of Isis and has been its Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. He serves as a director of Antisense Therapeutics Ltd., a biopharmaceutical company, Axon Instruments, Inc., a developer and manufacturer of novel high-technology devices and software for drug discovery, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. Dr. Crooke is also an adjunct professor of pharmacology at the University of California, San Diego, and San Diego State University.

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, Antisense Research since June 1995. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions.

RICHARD K. BROWN, PH.D.
Isis Vice President and President, GeneTrove

Dr. Brown has served as our President of 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 Director of our Development Chemistry department. Prior to joining Isis in 1991, Dr. Cole was Director of Chemical Affairs for Marion Laboratories.

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

Dr. Ecker was a founder of Isis 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
Vice President, Development

Dr. Levin is Vice President, Development. He leads Isis' research efforts to characterize the toxicity and pharmacokinetics of oligonucleotide-based therapeutic agents. Dr. Levin has managed more than 15 preclinical programs at Isis since joining the company in 1995. Prior to joining Isis, Dr. Levin worked at Hoffmann-La Roche Inc. where he was Research Leader in their Investigative Toxicology Department managing the Nuclear Receptor Research Group. During his tenure at Hoffman-LaRoche, Dr. Levin also established and supervised laboratories dedicated to the research of mechanisms of toxicity, biochemical toxicology and toxicokinetics.

PATRICIA LOWENSTAM
Vice President, Human Resources and Operations

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

ARON STEIN, PH.D.
Vice President, Regulatory Affairs and Quality Assurance

Dr. Stein has served as our Vice President, Regulatory Affairs and Quality Assurance since August 2002. Prior to joining Isis, Dr. Stein was Divisional Vice President of Medical and Regulatory Affairs, Hospital Products Division for Abbott Laboratories from September 1999 to August 2002, and Vice President in charge of Regulatory Affairs and Quality Assurance for SEQUUS Pharmaceuticals, Inc. from April 1997 to September 1999.

RISK FACTORS

Investing in our securities 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 securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

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, will be approved for commercialization or that our partners or we can successfully commercialize these drug candidates.

If the results of clinical testing indicate that any of our drugs under development, including Affinitak, 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. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications. In March 2003, we reported the results of our Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer. In this trial, Affinitak, when added to carboplatin and Paclitaxol, failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with the Affinitak trial Lilly is currently conducting as well as the trials for our other drugs.

If the market does not accept our products, 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, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially

available product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not succesfully commercialize additional products.

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

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

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

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

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;
- to conduct clinical trials; and
- successfully commercialize existing and future product candidates.

If any of our partners fail to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. Examples of terminated collaborations in 2002 include the termination of our HepaSense and Orasense collaborations with Elan and our collaboration with Merck to develop ISIS 113715. Although these collaborations terminated, we intend to continue developing the drugs that were the subject of the collaborations.

We are collaborating with Lilly to develop Affinitak, our most advanced drug candidate, with Lilly funding Affinitak's development. Lilly could decide to discontinue its funding of Affinitak. Based on the results of our recently completed Phase III clinical trial for Affinitak, or if the results of Lilly's Phase III clinical trial for Affinitak are not sufficient to support an NDA filing.

Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics, Limited and OncoGenex Technologies Inc. and Lilly with respect to ISIS 23722. If any of these pharmaceutical company partners does not continue to fund and/or develop these drug candidates, our business would suffer.

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.

In addition, the disappointing results of our recently completed Affinitak Phase III trial could cause our existing partners to reevaluate their commitment to our drug discovery platforms or could impair our ability to attract new collaborative partners. If any of our collaborative partners withdraw their resources or if we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

If our GeneTrove business cannot 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.

For example, in November 2002 we terminated our GeneTrove database product offering and reorganized our GeneTrove division. Consequently, we incurred a one-time charge of approximately $1.4 million associated with the restructuring during the fourth quarter of 2002.

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

Because drug discovery and development and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of December 31, 2002, our accumulated losses were approximately $460 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently derive our current product revenue 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, 2002, 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 do not meet our goals to

commercialize our drug products and research services or to license 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 target validation service and licensing program; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may have to cut back on one or more of our research, drug discovery or development programs 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 the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

If we cannot successfully operate our Affinitak manufacturing suite, the potential success of Affinitak, our revenues, and our relationship with Lilly could suffer.

Under a commercial supply agreement that we entered into with Lilly, we built a manufacturing suite to manufacture Affinitak. However, the FDA has not yet approved this manufacturing facility for

the manufacture of Affinitak, and there is no guarantee that we will receive this approval. We have limited experience in operating these types of facilities on a commercial scale and may not be able to successfully operate the manufacturing suite. If we fail to successfully operate the manufacturing facility or if the FDA does not approve the facility, we may be unable to commercialize or meet the potential demands for Affinitak. This could harm the success of Affinitak, reduce our revenue and disrupt our relationship with Lilly.

Specific difficulties we may encounter related to our manufacturing facility include:

- Governmental regulation of our manufacturing facility, specifically FDA approvals required for the commercial manufacture of Affinitak;
- Cost overruns;
- Reduced yields;
- Delays in the delivery of, or inferior quality of, key components of Affinitak that are supplied by third parties; and
- Other unforeseeable factors inherent in the manufacturing process.

In addition, our manufacturing experience to date has been limited to production of preclinical and clinical quantities of our product candidates and to limited commercial production of Vitravene. As a result, we may not be able to effectively scale-up our production in this facility to meet the potential demand for Affinitak. Therefore, we cannot be certain that our manufacturing facilities or our ability to sustain ongoing production of Affinitak will be able to meet our or Lilly's expectations.

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 other companies in the use of antisense technology, including siRNA, for gene target validation and gene functionalization, as well as with other technologies that are 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 cannot protect our patents or our proprietary rights, others may compete more directly against us.

Our success depends to a significant degree upon our ability to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive

advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

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.

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

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, 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. 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 the price of our securities would likely decrease.

For example, since the data from our Phase III trial for Affinitak were not sufficiently positive to support a single study NDA, we now must wait for the results of Lilly's ongoing Phase III Affinitak trial before we reevaluate whether the data are sufficiently positive to support filing an NDA for Affinitak. We do not expect results from this second Phase III trial until.

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. Failure to succeed in specific clinical trials, including the recently announced Phase III Affinitak results, may make it more challenging to recruit and retain qualified scientific personnel. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. If we cannot add these employees, we may not successfully achieve the goals of our Lilly collaboration.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our convertible notes. During the 12 months preceding December 31, 2002, the market price of our common stock has ranged from $6.00 to $22.40 per share. Since December 31, 2002 through March 25, 2003, the market price of our common stock has ranged from $2.50 to $7.55 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least $66^{2}/_{3}$% 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, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock which are currently outstanding and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these holders exercise their registration rights, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

If the private placement of our $5^{1}/_{2}$% convertible subordinated notes violated securities laws, purchasers in the private placement would have the right to seek refunds or damages.

On May 1, 2002, we issued and sold $125 million of $5^{1}/_{2}$% convertible subordinated notes due 2009 in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the

Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of the securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in the private offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

ITEM 2. Properties

As of February 28, 2003, we occupied approximately 218,000 square feet of laboratory and office space, including 6,888 square feet of manufacturing area built to meet Good Manufacturing Practices. We are primarily located in six buildings in Carlsbad, California. We own three of these buildings and, as of December 31, 2002, these buildings secured approximately $5.7 million of our debt. We lease three of the buildings under lease agreements, of which one lease expires in 2007 and two expire in 2010. In January 2002, we entered into a lease to secure an additional 37,400 square feet of space in Carlsbad, California. In September 2002, we further expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we expanded our manufacturing facility. We upgraded our existing manufacturing suite that is dedicated to the production of products for us and our non-Lilly partners. In addition, we added a second state-of-the-art manufacturing suite dedicated to Affinitak. Lilly provided us with funding in the form of a loan of up to $21 million, to build the Affinitak suite. We will repay the loan from Affinitak success milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan. In February 2003, we completed construction of the facility.

ITEM 3. Legal Proceedings

Not applicable.

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
2002		
First Quarter	$ 22.40	$ 14.07
Second Quarter	$ 18.00	$ 6.76
Third Quarter	$ 11.86	$ 6.10
Fourth Quarter	$ 11.00	$ 6.00
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, 2003, there were approximately 1,120 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Recent Sales of Unregistered Securities

Not applicable.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2002.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders	5,241,000(a)	$ 10.82	1,383,000(c)
Equity compensation plans not approved by stockholders	4,014,000(b)	$ 12.02	1,723,000
Total	9,255,000	$ 11.34	3,106,000

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

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

(c) Of these shares, 307,208 remain available for purchase under the 2000 Employee Stock Purchase Plan. The 2000 Employee Stock Purchase Plan incorporates an evergreen formula pursuant to which on each January 6 for the first 9 anniversaries, the aggregate number of shares reserved for issuance under the plan will be increased automatically by the lesser of (i) 1% of the total number of shares of Common Stock outstanding on such anniversary date or (ii) 200,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

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

As of December 31, 2002, there were 5,737,000 shares reserved for issuance under the 2000 Plan, options to purchase an aggregate of 4,014,000 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 253,000 shares had been exercised under the 2000 Plan, and 1,723,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the optionee's employment or service as a consultant or an affiliate.

If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), the 2000 Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the 2000 Plan, and the outstanding stock awards will be appropriately adjusted in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. The conversion of any of our convertible securities will not be treated as a transaction without receipt of consideration.

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

In the event of:

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

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, the vesting of such stock awards (and, if applicable, the time during which such stock awards may be exercised) will be

accelerated in full, and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event.

Available Information

We make available on our web site, *www.isispharm.com*, our 10-K, 10-Q's, 8-K's and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that is included on or linked to our Internet site is not a part of this report or any registration statement that incorporates this report by reference.

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

	Years Ended December 31,				
	2002	2001	2000	1999	1998
Statement of Operations Data:					
Revenues (includes amounts for R&D, licensing and	$ 80,179	$ 53,273	$ 37,255	$ 33,925	$ 39,171

royalties)					
Research and development expenses	$ 124,074	$ 83,741	$ 57,014	$ 66,413	$ 62,200
Net loss applicable to common stock	$ (73,302)	$ (75,131)	$ (54,699)	$ (59,645)	$ (42,983)
Basic and diluted net loss per share	$ (1.35)	$ (1.70)	$ (1.48)	$ (2.08)	$ (1.60)
Shares used in computing basic and diluted net loss per share	54,480	44,109	37,023	28,703	26,873

	December 31,				
	2002	2001	2000	1999	1998
Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 289,353	$ 312,018	$ 127,262	$ 52,839	$ 58,848
Working capital	$ 244,230	$ 280,569	$ 118,568	$ 44,213	$ 40,651
Total assets	$ 438,683	$ 417,061	$ 183,256	$ 103,107	$ 96,074
Long-term debt and capital lease obligations, less current portion	$ 192,893	$ 125,710	$ 102,254	$ 87,254	$ 77,724
Accumulated deficit	$ (459,893)	$ (386,591)	$ (311,460)	$ (256,761)	$ (197,116)
Stockholders' equity (deficit)	$ 155,477	$ 223,099	$ 66,366	$ 869	$ (4,186)

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

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into a broad pipeline of 12 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including inflammatory, viral, metabolic and dermatological diseases, and cancer, and we are studying these drugs in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene (fomivirsen) in 1998.

Affinitak, formerly LY900003 or ISIS 3521, is our most advanced product in development. We recently announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in overall survival of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone. Survival was the primary endpoint. The median survival for the Affinitak treated patients was ten months, compared to 9.7 months for those patients treated with the chemotherapy alone. Additional analyses of the data, however, suggest that Affinitak was active in this trial. For example, using an alternative statistical analysis of all 616 patients which considered predefined variables, including duration of treatment, survival of the Affinitak treated patients was greater than that of patients in the control group. This result was statistically significant. Lilly and we are performing an in-depth analysis of the data and expect to submit the complete findings from this trial for scientific presentation at an appropriate medical meeting later this year. Lilly plans to evaluate Affinitak's performance in its on-going Phase III trial, in which patients are being treated with Affinitak in combination with gemcitabine and cisplatin. As we proceed with these evaluations, Lilly and we will make a decision about the future development of Affinitak.

We currently have two Phase III clinical trials for another product, ISIS 2302, or alicaforsen, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America and Europe. We have five additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide important information about the function of genes. We use this information to direct our own drug discovery research and that of our antisense drug discovery partners, such as Lilly and Amgen. We generate this information rapidly and efficiently using the same proprietary methods and systems that we developed to create antisense drugs.

We offer anitsense-based gene function information to pharmaceutical company partners that are evaluating the genes as targets for their own drug discovery programs. Through the sale of this information, we generate revenue from our research efforts and increase industry experience with our technology. We are currently collaborating with ten major pharmaceutical partners, including Abbott Laboratories, Inc.; Amgen Inc.; Aventis; Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; GlaxoSmithKline plc; Johnson & Johnson Pharmaceutical Research & Development, LLC; Merck & Co., Inc. and Pharmacia Corporation. We also license our antisense-based functional genomics patents to partners. Through these license agreements, GeneTrove partners gain access to our functional genomics suite of patents for use in their internal genomics programs.

In August 2001, we added a subscription database product to GeneTrove's offerings. We were unsuccessful in generating customers for our database product and in November 2002 we announced its termination. This resulted in a reorganization of the GeneTrove division and a reduction in its workforce by approximately 25 people. The restructuring plan also provided for the write-down of certain intellectual property. Our GeneTrove division continues to generate near-term revenue while enhancing our own antisense drug discovery efforts and our patent portfolio.

Our Ibis division has invented platform technology that has the potential to revolutionize the detection and treatment of infectious disease. We are creating a sensor that can detect known and unknown infectious agents, and are working to discover small molecule drugs that work by binding to RNA. Our scientists have invented methods of identifying common binding sites in RNA that facilitate the identification of organisms or serve as targets for drug binding. We have also invented mass spectrometry-based screening methods for both diagnostic and drug discovery applications.

In a program called Triangulation Identification Genetic Evaluation of biological Risks, or TIGER, we are applying our Ibis technology to develop a sensor to detect infectious agents that could be used in biological warfare attacks. We are collaborating with San Diego-based Science Applications

International Corporation, or SAIC, on this multi-year program funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $9.8 million for its efforts related to TIGER.

Since the division's inception, Ibis has received significant financial support from various government agencies to use its technology to develop broad-spectrum anti-infective drugs that we believe will have usefulness in national defense. In early 2002, Ibis received a three-year contract to continue its drug discovery program with the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. The contract provides for funding of up to $2.4 million.

Critical Accounting Policies

We prepare our financial statements in conformity with accounting principles generally accepted in the United States. 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 upfront payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to upfront 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, Amgen, Antisense Therapeutics Limited, Chiron, and Pfizer.

We recognize revenue related to milestones upon completion of the milestone's performance requirement. During fiscal 2002, we earned milestones through our research collaborations with Amgen and Merck. In addition, in April 2002, we achieved a non-revenue development milestone in our HepaSense collaboration with Elan, which triggered a $3.8 million equity purchase by Elan of our common stock.

Revenue related to the sale of our inventory is generally recognized as we ship or deliver drugs to our partners. Occassionally, we complete the manufacturing of drugs, but are asked by our partner to deliver the drug on a later date. Under these circumstances, we ensure that our obligation is complete under the terms of the manufacturing agreement in place and title has transferred to the customer before we recognize the related revenue.

As part of our Lilly alliance, Lilly provided a $100 million interest-free loan to fund the joint research collaboration. As of December 31, 2002, we had drawn down $47.5 million on the $100 million loan. We discounted the $47.5 million to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We 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 related to the collaboration, and is recognized as revenue over the period of performance.

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. Examples of these agreements include Eyetech, Sequitur and most recently atugen.

Inventory Valuation

The value at which we carry our inventory directly impacts our results of operations. Our inventories primarily consist of drugs we manufacture for our partners under contractual terms. Our inventories are stated at the lower of cost or market, cost being determined under the first-in, first-out method. We review inventories periodically for potential items considered to be obsolete and adjust our carrying value to estimated net realizable value through an appropriate reserve. If our estimates of the market value of our inventory are more favorable than actual market conditions, we may be required to make inventory write-downs in the future.

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 primarily 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. We also have an ownership interest of less than 20% in two corporations we conduct business with, Antisense Therapeutics Limited and Hybridon. In determing if and when a decrease in market value below our cost is other-than-temporary in our equity positions, we examine historical trends in stock price, the financial condition and near term prospects of the issuer, and our current need for cash. When 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 impairment losses related to our short-term investments.

Use of Estimates

In preparing our financial statements to conform with accounting principles generally accepted in the United States, we make estimates and assumptions that affect the amounts reported in our financial statements and accompanying notes. These estimates include useful lives for fixed assets for depreciation calculations, useful lives for intellectual property for amortization calculations, estimated lives for license agreements related to deferred revenue, valuation of inventory, and assumptions for valuing stock options. Actual results could differ from these estimates.

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, Affinitak (formerly LY900003 or ISIS 3521) for non-small cell lung cancer, and formed a four year research collaboration. As part of the agreement, Lilly paid an upfront 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 Affinitak, and purchased $75 million of our common stock at $18 per share. The research collaboration loan is due in 2005 and, at our option, we can repay the loan at any time in cash or our common stock at $40 per share. In June 2002, Lilly and we expanded our antisense drug discovery collaboration to include gene targets associated with cancer. The expanded collaboration will focus on several antisense preclinical compounds, including ISIS 23722, directed at cellular regulators of cancer cell death, or apoptosis. At December 31, 2002 and 2001, Lilly owned approximately 7.55% and 7.75%, respectively, of our outstanding common stock.

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, 2002, we had drawn down $47.5 million on the $100 million research collaboration loan. We discounted the $47.5 million to its net present value by imputing interest on that amount at 20%, which represented market conditions in place at the time we entered into the loan. We are accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represents value given to us by Lilly to help fund the research collaboration, and is accounted for as deferred revenue and is recognized as revenue over the period of performance. For the years ended December 31, 2002 and 2001, the balances related to the research collaboration loan in long-term obligations and long-term deferred revenue were $28.0 million and $19.5 million, respectively, for 2002, and $9.7 million and $10.3 million, respectively, for 2001.

In September 2002, we further expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we upgraded and expanded our manufacturing facility. We added a new state-of-the-art manufacturing suite dedicated to Affinitak. Lilly provided us with funding in the form of a loan of up to $21 million, to build the Affinitak suite. We will repay the loan from Affinitak success milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan. In February 2003, we completed construction of the facility, which is located on our Carlsbad campus in an existing building.

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 provided 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 of credit 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.

In 2002, Elan and we agreed to extend the Orasense collaboration. Effective December 31, 2002, Elan concluded its participation in the Orasense collaboration in conjunction with its continuing

restructuring efforts. As a result, we have regained all rights to ISIS 104838, with a potential royalty due to Orasense. Orasense will distribute the royalty to Elan based on Elan's equity ownership in Orasense. This favorable outcome allows us to pursue further clinical development of ISIS 104838 and oral antisense drugs.

For the years ended December 31, 2002, 2001 and 2000, we recognized $8.9 million, $5.4 million, and $5.2 million, respectively, from Orasense as research and development revenues from affiliates. Additionally, we recorded $9.5 million, $10.3 million, and $9.7 million for the years ended December 31, 2002, 2001, and 2000, respectively, as equity in loss from affiliates related to Orasense. At December 31, 2002 and 2001 our balance sheet reflected $6.2 million and $1.7 million, respectively, under contracts receivable related to Orasense. During 2002 and 2001, we borrowed $0.9 million and $5.6 million, respectively, under a convertible promissory note payable to Elan to provide development funding to Orasense. In July 2002, we prepaid $11.8 million of the outstanding balance under the Orasense convertible promissory note. Based on the remaining principal and accrued interest outstanding at December 31, 2002, the loan balance due on its maturity date will be $9.4 million, provided that no further prepayments or conversions occur prior to maturity. The balance under this borrowing facility, including accrued interest, as of December 31, 2002 and 2001 was $7.2 million and $16.7 million, respectively, which approximated fair value. We cannot borrow any additional principal under the Orasense convertible promissory note. However, interest will continue to accrue on the outstanding amounts. The maturity date for the Orasense convertible promissory note is April 19, 2005.

In November 2002, Elan concluded its participation in the HepaSense collaboration in conjunction with its continuing restructuring efforts. As a result, we have regained all rights to ISIS 14803, with a potential nominal royalty due to HepaSense. HepaSense will distribute the royalty to Elan and us on a pro rata basis based on each parties' equity ownership in HepaSense.

For the years ended December 31, 2002, 2001 and 2000, we recognized $3.0 million, $5.2 million and $2.8 million, respectively, from HepaSense as research and development revenues from affiliates. Additionally, we recorded $6.5 million, $8.3 million, and $6.5 million for the years ended December 31, 2002,

2001 and 2000, respectively, as equity in loss from affiliates related to HepaSense. At December 31, 2001, our balance sheet reflected $2.5 million under contracts receivable related to HepaSense. There were no contracts receivable related to HepaSense at December 31, 2002. During 2002 and 2001, we borrowed $2.8 million and $2.6 million, respectively, under our HepaSense convertible promissory note with Elan to provide development funding to HepaSense. In July 2002, we prepaid the total principal and accrued interest of $7.9 million under the HepaSense convertible promissory note. There was no balance due under this borrowing facility at December 31, 2002 and we cannot borrow any additional funds against it. In comparison, at December 31, 2001, the balance was $4.8 million including accrued interest.

Results of Operations

Years Ended December 31, 2002 and December 31, 2001

Revenue

Total revenue for the year ended December 31, 2002 was $80.2 million, compared to $53.3 million for 2001. The increase of $26.9 million was primarily a result of increased research and development revenue under collaborative agreements. The most significant contributor was our strategic alliance with Lilly. The increase in total revenue was partially offset by a decrease in revenue from licensing and royalty revenue in 2002 from that reported in 2001.

Research and Development Revenue under Collaborative Agreements

Under the category research and development revenue under collaborative agreements, for the year ended December 31, 2002, we earned $67.8 million, compared to $40.4 million for 2001. The increase of $27.4 million was a result of several collaborations in place during 2002 which were in effect for only a part of 2001 or not in place during 2001. Our Lilly alliance, which we entered into in August 2001, significantly contributed to the increase in 2002 over 2001. Other sources of revenue present in 2002 but only in part or not at all in 2001 included: GeneTrove agreements with Amgen, atugen, Celera, Chiron, Merck, Pfizer and Pharmacia, as well as our Ibis division's October 2001 and March 2002 biological warfare defense research programs with DARPA and USAMRIID, respectively. In addition, during 2002 we earned a milestone under each of our antisense drug discovery collaborations with Amgen and Merck. The increase in revenue was partially offset by the June 2002 termination of our Ibis collaboration with Pfizer and a decrease in earned milestones in 2002 compared to 2001.

Research and Development Revenue from Affiliates

Research and development revenue from affiliates consisted of revenue associated with our two collaborations with Elan, Orasense and HepaSense. Elan concluded its participation in the HepaSense and Orasense collaborations in November 2002 and December 2002, respectively, in conjunction with its continuing restructuring efforts. During 2002, we recognized $8.9 million and $3.0 million from Orasense and HepaSense, respectively, as revenue. During 2001, we recognized $5.4 million and $5.2 million as revenue from Orasense and HepaSense, respectively. The increase in revenue from the Orasense collaboration was primarily due to the progression of ISIS 104838 into later stages of clinical development. The decrease in revenue from the HepaSense collaboration was primarily due to the conclusion of the collaboration during the second half of 2002. As part of its restructuring activities, Elan concluded its participation in the Orasense collaboration at the end of 2002.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $417,000 for the year ended December 31, 2002, compared with $2.3 million in 2001. The primary source of the revenue reported in 2002 was our licenses with Roche Molecular and Proligo. The decrease of $1.9 million in 2002 from that reported for 2001 was primarily related to one-time revenue recorded in 2001 associated with a $2.0 million license fee paid to us by Eyetech Pharmaceuticals, Inc., a privately held company.

Operating Expenses

Total operating expenses were $131.0 million and $99.4 million for the years ended December 31, 2002 and 2001, respectively. The increase of $31.6 million was the result of increased research and development activities to support the various products we had in development during 2002 and our research collaborations with Lilly and Amgen. Furthermore, the drug we delivered and expensed in 2002, offset by the capitalization of inventory, resulted in additional research and development expense of $2.2 million. The increase in operating expenses was partially offset by a decrease in general and administrative expenses, and a reversal of compensation expense related to variable stock options due to the decrease in market value of our stock.

Research and Development Expenses

For the year ended December 31, 2002, we reported total research and development expenditures of $124.1 million, compared to $83.7 million reported in 2001. The $40.4 million increase in 2002 over 2001 was primarily due to our investment in the various products we had in development during 2002, including three Phase III clinical trials, costs associated with our Lilly and Amgen research

collaborations, and costs associated with increased gene functionalization and target validation activities in support of our numerous GeneTrove collaborations.

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.

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. 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. In November 2002, we terminated our GeneTrove database product offering and reorganized the GeneTrove division.

We incurred a one-time charge of approximately $1.4 million associated with this restructuring in the fourth quarter of 2002. Although we are no longer offering our GeneTrove database to customers, we continue to offer gene functionalization and target validation services to pharmaceutical and biotechnology companies. Further, we continue to perform these activities as part of our internal antisense drug discovery efforts. We would expect that cost savings from the termination of our GeneTrove database would likely be offset by increases in gene functionalization and target validation services for our in house drug discover programs and our existing and future partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology. Through the efforts of our scientists in the antisense drug discovery group, we have produced second-generation antisense drugs that have been shown to have increased potency, increased stability, an improved side effect profile and the potential for oral administration. With more than a decade focused on learning the capabilities of antisense technology and how these compounds behave in the body, our scientists have learned the organs and tissues in humans to which antisense therapy is effectively directed. Using this knowledge, we have strategically focused our research programs on those sites in the body that accept antisense readily 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 and Amgen.

As we expand our research programs into new sites in the body and new disease categories, 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, 2002 totaled $38.9 million compared to $20.9 million for 2001. The increase was principally a result of a full year's activity related to the Lilly research collaboration, the September 2002 expansion of the Lilly research collaboration to include oncology, and the advancement of research related to our Amgen 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, with the length

varying 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 a 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. Currently we have 12 drug candidates in various stages of development including two drugs in Phase III clinical trials. We recently announced the results of our Phase III clinical trial of Affinitak for the treatment of non-small cell lung cancer. In this trial, we observed no difference in overall survival of those patients who received Affinitak plus a standard chemotherapy regimen compared to those patients who received the standard chemotherapy alone. Survival was the primary endpoint. The median survival for the Affinitak treated patients was ten months, compared to 9.7 months for those patients treated with the standard chemotherapy alone. Based on these results we will not file an NDA for Affinitak in 2003. We expect a decrease in Affinitak related expenses in 2003 compared to 2002. We have two Phase III trials of Isis 2302, or alicaforsen, in people with active Crohn's disease. One is enrolling patients in North America and the other in Europe. These studies are evaluating the safety and efficacy of alicaforsen. Additionally, we have five products in Phase II trials, one product in Phase I trials and four 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 Affinitak, we received an upfront license payment, which helped fund the costs we incurred during 2001 for our current Phase III trial. In addition, Lilly reimburses us for our costs related to the continued development of Affinitak.

Historically, we had expensed drug manufacturing costs as they were incurred. In 2002, to reflect the advancement of our pipeline into later stages of clinical development and as a result of the increasing number of clinical supply agreements where we sell drugs that we manufacture to partners, we began capitalizing the related manufacturing costs for our drugs. We expense manufacturing costs when we deliver our drugs to partners and as we use our drugs in our own clinical trials. This may result in period to period differences in operating expenses related to the volume of drug production and the timing of drug shipments. In September 2002, we agreed to manufacture Affinitak during the product launch period for Lilly. Under the terms of the agreement, we may produce Affinitak for commercial use for approximately three years, after which Lilly plans to assume responsibility for manufacturing.

Development expenditures totaled $55.3 million and $37.9 million for the years ended December 31, 2002 and 2001, respectively. The increase of $17.4 million reflects the expansion and advancement of our pipeline. During 2002, we had 13 products in development including two products, Affinitak and alicaforsen for Crohn's disease, in Phase III clinical trials and six products in Phase II clinical trials. Expenditures related to Affinitak in 2002 totaled $22.6 million, compared to $11.5 million in 2001. The increase of $11.1 million in 2002 over 2001 was a result of delivery of Affinitak drug to Lilly for use in clinical trials, expenses for our Phase III trial of Affinitak and the advancement of our various Phase II trials for Affinitak.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $4.8 million for the year ended December 31, 2002, compared to $3.4 million for the same period of 2001. The increase of $1.4 million for the year ended December 31, 2002 over the same period in 2001 is a result of our two Phase III trials initiated in November 2001 and June 2002, in the United States and Europe, respectively.

Expenditures related to our other products in development totaled $23.1 million in 2002 compared to $16.2 million in 2001. The increase of $6.9 million in 2002 over 2001 was a result of the development of the other antisense products in our pipeline, including expenses related to the initiation of our Phase II clinical

trials for alicaforsen for Ulcerative Colitis, ISIS 14803 and ISIS 104838 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. Costs for these items have increased since Ibis expanded the application of its technology to develop a sensor to detect infectious agents. 2002 was the first full year for these efforts.

Since its inception, Ibis has received significant financial support from various government agencies to advance its technology for the detection and treatment of infectious disease. From June 2000 through June 2002, Ibis also received funding, including two research milestones totaling $4.0 millon, from its collaboration with Pfizer, which ended in June 2002 in accordance with the terms of the agreement.

Ibis expenditures for the year ended December 31, 2002 totaled $8.3 million, compared to $6.5 million in 2001. The increase of $1.8 million was primarily related to Ibis' performance obligations under its multi-year government contracts with DARPA awarded in October 2001 and USAMRIID awarded in March 2002.

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 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 17% 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 2002 these costs were a smaller percentage of total research and development expenses than in 2001.

R&D Support costs for fiscal year 2002 totaled $21.6 million, compared to $18.4 million for 2001. The increase of $3.2 million is a direct result of increases in our research and development efforts. While we work to control R&D Support costs, we expect that they will increase as direct research and development costs increase. We expect R&D Support costs will increase in 2003 as we perform under our Lilly collaboration, our government contracts, our GeneTrove collaborations and advance our pipeline.

General and Administration Expenses

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 finance. 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 $8.5 million in 2002 compared to $11.1 million for the same period of 2001. This $2.6 million decrease is the result of certain costs previously included in general and administrative expenses, which we have determined are more accurately reflective of research and development efforts.

Compensation Related to Stock Options

In 2002, we reversed $3.0 million of expense previously recorded in 2001 related to variable stock options. For the year ended December 31, 2001, we reported $4.6 million as compensation expense related to stock options. The compensation related to stock options 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 decrease of $7.6 million in 2002 over 2001 was primarily a result of the 70% decrease in the price of our common stock at of December 31, 2002 compared to its price at December 31, 2001. In addition, we account for stock options granted to consultants in accordance with EITF 96-18, which contributed to the expense recorded in 2002 and 2001. At December 31, 2002, all of the options exchanged in January 2000 were either exercised or cancelled.

Restructuring Activities

In November 2002, we announced the termination of the GeneTrove database product offering and the reorganization of the GeneTrove division. As a result, we reduced our workforce by approximately 25 people. The restructuring plan included the write-down of certain intellectual property valued at $597,000. As of December 31, 2002, we incurred a one-time charge of $1.4 million for restructuring activities. There were no restructuring charges in 2001.

Equity in Loss of Affiliates

Equity in loss of affiliates for the year ended December 31, 2002 was $16.0 million compared to $18.8 million for the year ended December 31, 2001. 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 as equity in loss of affiliates. As of December 31, 2002, our equity in loss of affiliates from Orasense and HepaSense totaled $9.5 million and $6.5 million, respectively. In comparison, our equity in loss of affiliates as of December 31, 2001 was $10.3 million for Orasense and $8.3 million for HepaSense.

In 2002, Elan and we agreed to extend the Orasense collaboration. Effective December 31, 2002 Elan concluded its participation in the Orasense collaboration in conjunction with its continuing restructuring efforts. As a result, we have regained all rights to ISIS 104838, with a potential royalty due to Orasense. Orasense will distribute the royalty to Elan based on Elan's equity ownership in Orasense. This favorable outcome allows us to pursue further clinical development of ISIS 104838 and oral antisense drugs.

In November 2002, Elan concluded its participation in the HepaSense collaboration in conjunction with its continuing restructuring efforts. As a result, we have regained all rights to ISIS 14803, with a potential nominal royalty due to HepaSense. HepaSense will distribute the royalty to Elan and us on a pro rata basis based on each parties' equity ownership in HepaSense.

Investment Income

For the years ended December 31, 2002 and 2001, investment income was $8.5 million and $6.4 million, respectively. Although our ending cash balance decreased slightly in 2002 compared to 2001, our average cash balance was significantly higher, which favorably affected our investment 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 for the year ended December 31, 2002 was $16.6 million compared to $15.2 million for the same period in 2001. Interest expense increased by $1.4 million in 2002 over 2001, primarily as a result of interest accrued on the May 1, 2002 issuance of $125 million of $5^1/_2$% convertible subordinated notes and increased borrowings under the $100 million loan that Lilly made available to fund the research collaboration. Offsetting these increases was the reduction in interest expense from the prepayment in May 2002 of our 14% Senior Subordinated Notes and a portion of our Elan convertible notes for Orasense and HepaSense. The 14% Senior Subordinated Notes and a portion of the Elan convertible notes were prepaid in May 2002 and July 2002, respectively, resulting in a $2.3 million loss and $5.0 million gain, respectively.

In 2002, $8.6 million of the $16.6 million in interest expense, which was accrued under various long-term debt agreements, did not require cash payments. The long-term debt agreements with deferred interest and principal payments include our $100 million loan from Lilly and the remaining portion of our Elan line of credit for Orasense.

Loss on Prepayment of 14% Notes

For the year ended December 31, 2002, we reported a $2.3 million loss, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest, on the prepayment of approximately $74.0 million of our 14% Senior Subordinated Notes. The loss was recorded in the second quarter of 2002.

Gain on Prepayment of 12% Notes

In July 2002, we used $14.7 million in cash to prepay $19.7 million of 12% convertible debt held by Elan. As a result, we reported a $5.0 million gain on prepayment of debt for the year ended December 31, 2002. The gain was recorded in the third quarter of 2002.

Net Loss Applicable to Common Stock

For the year ended December 31, 2002 and 2001, we reported a net loss of $72.2 million and $73.8 million, respectively. Our net loss applicable to common stock was $73.3 million for the year ended December 31, 2002, and $75.1 million in 2001, which include $1.1 million and $1.3 million of accreted dividends on preferred stock as of December 31, 2002 and 2001, respectively. The decrease in accreted dividends in 2002 from 2001 was the result of the August 2002 conversion of 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of our common stock using a conversion price of $12.54 per share. Included in the conversion were approximately $2.1 million in preferred stock dividends accrued in prior years.

Net Operating Loss Carryforward

At December 31, 2002, our net operating loss carryforward for federal income tax purposes was approximately $370.2 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 $28.1 million as of December 31, 2002. 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, 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 revenue 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 entered into in August 2001. Also contributing to the increase in total revenue was research and development revenue 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 revenue in 2001 from that reported in 2000.

Research and Development Revenue under Collaborative Agreements

Under the category research and development revenue 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 was a result of 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, Affinitak. In May 2001, we entered into an agreement with Merck in which we licensed our preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. In December 2002, we reacquired the rights to ISIS 113715 from Merck. Other sources of research & development 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 Revenue 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 was 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 Revenue

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 paid 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 was primarily related to one-time revenue recorded in 2000 associated with the sale of certain patents to Coley Pharmaceuticals Group.

Operating Expenses

Our total operating expenses, which include 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 primarily resulted from our increased research and development expenditures. Also contributing to the increase was expense recorded under compensation related to stock options and an increase in our general and administrative expenditures. The increase was partially offset by the absence of restructuring activities present in 2000.

Research and Development Expenses

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 various 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

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

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 reflected 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, Affinitak and alicaforsen, 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 Affinitak in 2001 totaled $11.5 million, compared to $6.9 million in 2000. The increase of $4.6 million in 2001 over 2000 was a result of a full year of expenses for our Phase III trial of Affinitak and the advancement of our Phase II trials for Affinitak.

Our second Phase III drug, alicaforsen, 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 alicaforsen at doses higher than previously studied in our controlled trials, which were ongoing in 1999.

Ibis

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 October 2001.

R&D Support

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.

General and Administration

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.

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. 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.

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 was 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. The increase was offset by a change away from equity method accounting for our investment in Pantheco due to a decrease in our ownership of Pantheco. During 2000, we expanded our agreement with 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 and our investment declined 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 was primarily related to debt arrangements where interest and principal payments were deferred. Interest and principal payments were deferred on our $40.0 million debt financing initiated in 1997 and 1998, and our borrowings under the Elan convertible promissory notes for our Orasense and HepaSense collaborations. 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 convertible promissory notes, respectively. Also contributing to the increase during 2001 were the effects of borrowing $20 million under the $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 included $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.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2002, we have earned approximately $350.5 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 $587.4 million from the sale of equity securities. We have borrowed approximately $290.6 million under long-term debt arrangements to finance a portion of our operations.

At December 31, 2002, we had cash, cash equivalents and short-term investments of $289.4 million and working capital of $244.2 million. In comparison, we had cash, cash equivalents and short-term investments of $312.0 million and working capital of $280.6 million as of December 31, 2001. The decrease in our cash, cash equivalents and short-term investments, and working capital was primarily due to cash used to fund operating activities and the prepayment of $74.0 million and $19.7 million of debt in the second and third quarters of 2002, respectively, offset by the net proceeds we received from the issuance in the second quarter of $125.0 million of convertible notes. Other significant cash uses in 2002 included $36.8 million for construction of a manufacturing facility for Affinitak, expansion of our existing manufacturing facility for our other drugs in development and the purchase of property and equipment. In addition, significant uses of cash included $9.5 million related to our investments in our affiliates, $4.7 million related to our expanding patent estate, and $3.9 million in principal payments on our debt and capital lease obligations.

In September 2002, we agreed to manufacture Affinitak during the product launch period for Lilly. Lilly has provided us with a loan of up to $21 million to fund the construction of the new manufacturing facility for Affinitak mentioned above. At December 31, 2002, we had drawn down

$15.4 million under this loan. We expect to draw down the remaining amount under the loan in the first half of 2003. We will repay the loan from Affinitak success milestones due from Lilly or other product-related cash flows. The loan is secured with the movable equipment purchased for the manufacturing facility.

At December 31, 2002, our long-term obligations totaled $192.9 million, versus $125.7 million at December 31, 2001. In May 2002, we increased our long-term obligations by completing a convertible debt offering of $125.0 million of 5 1/2% convertible subordinated notes due May 2009, which raised approximately $120.9 million, net of issuance costs. The $4.1 million of debt issuance costs was included in our statement of cash flows for the year ended December 31, 2002 in the line item titled licenses and other assets. We used $74.0 million of the proceeds from this debt offering to prepay 14% debt. The prepayment of debt resulted in a payment of $40.0 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. The $32.6 million of interest expense related to the prepayment of this debt was included in our statement of cash flows for the twelve months ended December 31, 2002 in the line item titled accrued interest on prepayment of debt. The $40.0 million of principal related to this debt prepayment was included under financing activities in the line item titled principal payments on prepayment of debt.

In July 2002, we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5.0 million, which was recorded in the third quarter of 2002 as a gain on prepayment of 12% notes. Of the $19.7 million prepayment, $2.1 million was for accrued interest and was included in our statement of cash flows for the year ended December 31, 2002 in the line item titled accrued interest on prepayment of debt. As of December 31, 2002, the combined carrying amount of the remaining notes not prepaid in July 2002 was $7.2 million. For a more detailed explanation of these notes, see Note 3 to the Financial Statements, "Long-term Obligations and Commitments."

In 2001, Lilly made available to us a $100 million interest-free loan, to be used for the joint research collaboration. As of December 31, 2002, we had drawn down $47.5 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, we can repay the loan in either cash or with 2.5 million shares of our common stock at a fixed conversion price of $40 per share.

We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We expect to continue to use lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of December 31, 2002. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in 000s)				
Contractual Obligations	**Total**	**Less than 1 year**	**2 - 3 years**	**4 - 5 years**	**After 5 years**
Debt	$ 206,069	$ 17,834	$ 42,943	$ 4,938	$ 140,354
Capital Lease Obligations	$ 8,259	$ 3,602	$ 4,657	$ —	$ —
Operating Leases	$ 14,384	$ 2,505	$ 4,428	$ 3,772	$ 3,679

We plan to continue to make 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, like issuing additional shares of our common stock,

issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at December 31, 2002 combined with investment income and committed contractual cash payments from our partners will be sufficient to meet our anticipated cash requirements for at least the next 36 months. Due to the uncertainties in our business discussed in this section, and within "Risk Factors," beginning on page 27, this may not be the case. 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 15(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 25, 2003 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2003 Annual Meeting of stockholders to be held on June 10, 2003.

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 "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

ITEM 11. Executive Compensation

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

ITEM 12. Security Ownership of Certain Beneficial Owners and Management

The information required by this item is incorporated by reference to the information under the caption "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" 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.

ITEM 14. Controls and Procedures

For the period ended December 31, 2002, an evaluation was performed under the supervision and with the participation of our management, including the Chief Executive Officer (CEO) and the Chief Financial Officer (CFO), of the effectiveness of the design and operation of our disclosure controls and procedures. Based on that evaluation, our management, including the CEO and CFO, concluded that our disclosure controls and procedures were effective as of December 31, 2002. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to December 31, 2002.

PART IV

ITEM 15. 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 61 through 66.

(b) Reports on Form 8-K

On November 20, 2002, the Registrant filed a report on Form 8-K to announce it had regained rights to ISIS 14803, in connection with the termination of a collaboration with Elan Corporation, plc related to the HepaSense Ltd joint venture. Additionally, the Registrant announced that a second collaboration with Elan

was amended and the Orasense Ltd joint venture was extended through the end of 2002. The agreements were dated October 24, 2002 and filed with the related press release dated November 6, 2002.

(c) Exhibits

The exhibits required by this Item are listed under Item 15(a)(3).

(d) Financial Statement Schedules

The financial statement schedules required by this Item are listed under Item 15(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 31st day of March, 2003.

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. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	March 31, 2003
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 31, 2003
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 31, 2003

/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 31, 2003
/s/ WILLIAM R. MILLER William R. Miller	Director	March 31, 2003
/s/ FREDERICK T. MUTO Frederick T. Muto	Director	March 31, 2003
/s/ JOHN C. REED	Director	March 31, 2003

John C. Reed, M.D., Ph.D.		
/s/ MARK B. SKALETSKY		
Mark B. Skaletsky	Director	March 31, 2003
/s/ JOSEPH H. WENDER		
Joseph H. Wender	Director	March 31, 2003

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this annual report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the "Evaluation Date"); and

   c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this annual report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: March 31, 2003

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

CERTIFICATION

I, B. Lynne Parshall, certify that:

1.

I have reviewed this annual report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

a) designed such disclosure controls and procedures to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the "Evaluation Date"); and

c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) all significant deficiencies in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this annual report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: March 31, 2003

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, Esq.
Chief Financial Officer

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001.(19)
3.3	Bylaws.(19)
4.1	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. (20)
4.15	Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.16	Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.17	Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(16)
4.18	Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 5 1/2% Convertible Subordinated Notes due 2009.(16)
4.19	Form of 5 1/2% Convertible Subordinated Note due 2009.(16)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2*	Registrants 1989 Stock Option Plan, as amended.(6)
10.3*	Registrants 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. (23)
10.5*	Registrants Employee Stock Purchase Plan.(10)
10.6	Form of Employee Assignment of Patent Rights.(1)
10.7*	Registrants 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.8	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(3)
10.9	Agreement between the Registrant and CIBA Vision Corporation (now Novartis Ophthalmics AG) dated July 10, 1997 (with certain confidential information deleted).(5)
10.10	Amendment No. 2 to the Agreement between the Registrant and CIBA Vision Corporation dated September 14, 1998 (with certain confidential information deleted).(8)
10.11	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)
10.12	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)
10.13	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)
10.14	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)
10.15	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.16	Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted).(7)
10.17	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.18	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)
10.19	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant; together with related Amendment to the Stock Purchase Agreement.(13)
10.20	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)
10.21	Agreement between the Registrant and Agouron Pharmaceuticals dated June 9, 2000 (with certain confidential information deleted).(15)
10.22	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.23	Agreement between the Registrant and Merck & Co., Inc., dated May 22, 2001 (with certain confidential information deleted).(19)

10.24	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential

	information deleted).(19)
10.25	Agreement between the Registrant and PE Corporation through the Celera Genomics Group, dated July 9, 2001 (with certain confidential information deleted).(19)
10.26	Collaboration Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(20)
10.27	Development and License Agreement, dated August 14, 2001 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(20)
10.28	Affinitak 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).(20)
10.29	Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.30	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.31	Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.32	Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.33	Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.34	Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc.(22)
10.35	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.36	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.37	Collaboration Agreement dated December 11, 2001 between the Registrant and Amgen Inc.(24)
10.38	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.39	Amendment No. 1 to Securities Purchase Agreement dated January 14, 2000, between the Registrant and Elan International Services, Ltd. (with certain confidential information deleted).(27)
10.40	Amendment No. 2 to Agreement between the Registrant and Merck & Co., dated April 19, 2002 (with certain confidential information deleted).(27)
10.41	Letter Agreement dated April 24, 2002 between the Registrant and Reliance Insurance Company.(26)
10.42	Amended and Restated Collaboration Agreement dated June 17, 2002, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(27)
10.43	Settlement, Release, and License Grant Agreement dated September 6, 2002, between the Registrant and Sequitur, Inc. (with certain confidential information deleted).(28)
10.44	Revised and Restated ISIS 3521 Supply Agreement dated September 30, 2002, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(29)
10.45	Loan Agreement dated September 30, 2002, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(29)

10.46	Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.47	Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.48	Amended and Restated Subscription, Joint Development and Operating Agreement among the Registrant, Elan Corporation, Plc., Elan International Services, Ltd. and Orasense Ltd., dated October 24, 2002 (with certain confidential information deleted).(30)
10.49	Termination Agreement among the Registrant, Elan Corporation, Plc., Elan Pharma International Limited, Elan International Services, Ltd. and HepaSense Ltd., dated November 5, 2002.(30)
10.50	Registrant's restated 10b5-1 Trading Plan.
10.51	Registrant's 2002 Non-Employee Directors' Stock Option Plan.(31)
10.52	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(31)
10.53	Amendment to Collaborative Research and License Agreement dated April 22, 2002 between the Registrant and PE Corporation through the Celera Genomics Group.
10.54	Amendment No. 2 to Collaborative Research and License Agreement dated January 22, 2003 between the Registrant and PE Corporation through the Celera Genomics Group.
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 57.
99.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)

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

(2) Filed as an exhibit to 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. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference

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

(18) Filed as 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 report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.

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

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

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

(23) 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.

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

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

(26) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended March 31, 2002 and incorporated herein by reference.

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

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

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

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

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

* 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, 2002 and 2001, and the related statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2002. 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, 2002 and 2001, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2002, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

San Diego, California
January 30, 2003

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS

(in thousands, except share data)

	December 31, 2002	December 31, 2001
ASSETS		
Current assets:		
Cash and cash equivalents	$ 101,856	$ 127,011
Short-term investments	187,497	185,007
Contracts receivable	14,906	10,360
Inventory	11,090	—
Other current assets	4,831	6,438
Total current assets	320,180	328,816
Property, plant and equipment, net	59,094	28,245
Licenses, net	30,749	32,361
Patents, net	18,904	16,735
Investments in affiliates	—	1,307
Deposits and other assets	9,186	5,298
Long-term investments	570	4,299
Total assets	$ 438,683	$ 417,061
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,524	$ 6,126
Accrued compensation	3,330	5,646
Accrued liabilities	6,794	3,942
Amount due to affiliates	5,193	—

Current portion of long-term obligations	21,435	9,837
Current portion of deferred contract revenues	33,674	22,696
Total current liabilities	75,950	48,247
5 1/2% convertible subordinated notes	125,000	—
Long-term obligations, less current portion	67,893	125,710
Long-term deferred contract revenue, less current portion	14,363	20,005
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, zero and 120,150 shares authorized, issued and outstanding at December 31, 2002 and 2001, respectively	—	12,015
Accretion of Series A Preferred stock dividends	—	1,711
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 issued and outstanding at December 31, 2002 and 2001	12,015	12,015
Accretion of Series B Preferred stock dividends	1,866	1,222
Common stock, $.001 par value; 100,000,000 shares authorized 55,215,785 and 53,750,318 shares issued and outstanding at December 31, 2002 and 2001, respectively	55	54
Additional paid-in capital	602,101	582,258
Deferred compensation	(59)	(245)
Accumulated other comprehensive income (loss)	(608)	660
Accumulated deficit	(459,893)	(386,591)
Total stockholders' equity	155,477	223,099
Total liabilities and stockholders' equity	$ 438,683	$ 417,061

See accompanying notes

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

	Years Ended December 31,		
	2002	2001	2000
Revenue			
Research and development revenue under collaborative agreements	$ 67,820	$ 40,396	$ 16,912
Research and development revenue from affiliates	11,942	10,561	7,967
Licensing and royalty revenue	417	2,316	12,376
Total revenue	80,179	53,273	37,255
Expenses			
Research and development not including compensation (benefit) related to stock options of ($2,018), $3,244, and $435 in 2002, 2001 and 2000, respectively	124,074	83,741	57,014
General and administrative not including compensation (benefit) related to stock options of ($984), $1,329, and $152 in 2002, 2001, and 2000, respectively	8,547	11,061	8,644
Compensation (benefit) related to stock options	(3,002)	4,573	587
Restructuring activities	1,373	—	1,635
Total operating expenses	130,992	99,375	67,880
Loss from operations	(50,813)	(46,102)	(30,625)
Equity in loss of affiliates	(16,011)	(18,840)	(16,224)
Investment income	8,462	6,358	6,524
Interest expense	(16,562)	(15,248)	(13,160)
Loss on prepayment of 14% Notes	(2,294)	—	—
Gain on prepayment of 12% Notes	4,976	—	—

Net loss	(72,242)	(73,832)	(53,485)
Accretion of dividends on preferred stock	(1,060)	(1,299)	(1,214)
Net loss applicable to common stock	$ (73,302)	$ (75,131)	$ (54,699)
Basic and diluted net loss per share	$ (1.35)	$ (1.70)	$ (1.48)
Shares used in computing basic and diluted net loss per share	54,480	44,109	37,023

See accompanying notes

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY

Years Ended December 31, 2002, 2001 and 2000

(in thousands)

	Preferred stock			Common stock						
Description	**Shares**	**Amount**	**Dividend Accretion**	**Shares**	**Amount**	**Additional paid in capital**	**Deferred compensation**	**Accumulated other comprehensive income/(loss)**	**Accumulated deficit**	**Total Stockholders' Equity**
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 and Employee 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 of offering costs	—	—	—	12,760	13	218,213	—	—	—	218,226
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
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(73,302)	(73,302)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(1,268)	—	(1,268)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(74,570)

Dividends accrued on preferred stock	—	—	1,060	—	—	—	—	—	—	1,060
Deferred compensation	—	—	—	—	—	(3,188)	3,188	—	—	—
Options exercised and employee stock purchase plan	—	—	—	683	1	5,139	—	—	—	5,140
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(3,002)	—	—	(3,002)
Issuance of common stock	—	—	—	126	—	3,750	—	—	—	3,750
Conversion of preferred stock into common stock	(120)	(12,015)	(2,127)	657	—	14,142	—	—	—	—
Balance at December 31, 2002	12	$ 12,015	$ 1,866	55,216	$ 55	$ 602,101	$ (59)	$ (608)	$ (459,893)	$ 155,477

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS

(in thousands)

	Years Ended December 31,		
	2002	2001	2000
Operating activities:			
Net loss	(72,242)	$ (73,832)	$ (53,485)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	10,304	6,967	5,535
Compensation (benefit) related to stock options	(3,002)	4,573	587
Deferred interest on long-term debt	8,634	12,017	9,685
Loss on prepayment of 14% notes	2,294	—	—
Gain on prepayment of 12% notes	(4,976)	—	—
Accrued interest on prepayment of debt	(34,706)	—	—
Equity in losses of affiliates	16,011	18,840	16,224
Loss of investments	—	515	—
Equity in affiliate received in exchange for patent licensing	—	—	(1,125)
Write-off of patents	1,622	157	—
Write-off of inventory	—	—	301
Gain on disposal of property, plant and equipment	(260)	(570)	—
Changes in operating assets and liabilities:			
Contract receivable	(4,546)	(7,014)	2,083
Inventory	(11,090)	—	
Other current assets	6,226	(1,842)	(1,604)
Accounts payable	(2,147)	3,796	(917)
Accrued compensation	(2,316)	2,048	2,383
Accrued liabilities	2,812	2,943	(1,458)
Deferred contract revenues	(6,999)	25,244	(1,395)
Net cash used in operating activities	(94,381)	(6,158)	(23,186)
Investing activities:			
Purchase of short-term investments	(200,563)	(334,032)	(312,436)
Proceeds from the sale of short-term investments	196,075	236,236	242,487
Purchases of property, plant and equipment	(36,834)	(9,287)	(1,649)
Proceeds from the disposal of property, plant and equipment	—	500	—
Licenses and other assets	(9,536)	(28,674)	(3,182)
Investments in affiliates	(9,511)	(8,229)	(20,599)
Net cash used in investing activities	(60,369)	(143,486)	(95,379)
Financing activities:			
Net proceeds from issuance of equity	8,890	210,458	118,240
Proceeds from 5.5% convertible subordinated notes	125,000	—	—
Proceeds from long-term borrowing	52,334	31,363	8,583
Principal payments on prepayment of debt	(52,704)	—	—
Principal payments on debt and capital lease obligations	(3,925)	(4,781)	(3,939)

Net cash provided by financing activities	129,595	237,040	122,884
Net increase (decrease) in cash and cash equivalents	(25,155)	87,396	4,319
Cash and cash equivalents at beginning of year	127,011	39,615	35,296
Cash and cash equivalents at end of year	$ 101,856	$ 127,011	$ 39,615
Supplemental disclosures of cash flow information			
Interest paid	$ 39,333	$ 3,514	$ 3,454
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt for patent acquisitions	$ —	$ 13,500	$ —
Additions to debt for licensing costs	$ 1,050	$ —	$ —
Additions to deposits and other assets from sale of equipment	$ 300	$ —	$ —
Additions to other current assets from sale of equipment	$ 160	$ —	$ 27
Repayment of debt with common stock	$ —	$ 15,000	$ —
Conversion of preferred stock into common stock	$ 14,142	$ —	$ —
Addition to obligations of 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, 2002

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 are 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 20.3 million at December 31, 2002 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, 2002, 2001 and 2000, diluted common equivalent shares were not included in the computation of diluted net loss per share because the effect would be antidilutive.

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and is recorded as earned based on the performance requirements of the collaborative research and development contracts. Contract fees for which no further performance obligations exist is recognized when the payments are received or when the collection is assured. Payments received in excess of amounts earned are recorded as deferred contract revenue. Research and development costs are expensed as incurred. For the years ended December 31, 2002, 2001 and 2000, research and development costs and expenses of approximately $68.3 million, $59.2 million and $28.4 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 revenue under collaborative agreements

Research and development revenue under collaborative agreements is recognized as the related expenses are incurred, up to contractual limits. Payments received under these agreements that relate to future performance are deferred and recorded as revenue earned over their specified future performance period. Revenue that relates to nonrefundable, upfront fees is recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue that relates to milestones is recognized upon completion of the milestone's performance requirement. Isis recognizes revenue from federal research grants during the period in which the related expenditures are incurred. Revenue from our Vitravene product sales is recognized when the product is shipped. Revenue associated with our clinical product sales is recognized when product is delivered.

As part of the Company's alliance with Eli Lilly and Company (Lilly), Lilly provided a $100.0 million interest-free loan to fund the research collaboration. As of December 31, 2002, Isis had drawn down $47.5 million on the $100.0 million loan. Isis discounted the $47.5 million to its net present value by imputing

interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis is 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 Isis by Lilly to help fund the research collaboration, and Isis is accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance.

Research and development revenue from affiliates

Research and development revenue from affiliates is recognized as the related expenses are incurred, up to contractual limits. Revenue related to milestones is recognized upon completion of the milestone's performance requirement, unless consideration for achievement of the milestone is in cash in exchange for the Company's common stock.

Licensing and royalty revenue

Licensing and royalty revenue 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 SFAS 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 for more detail on the Company's investments.

Inventory Valuation

The value at which Isis carries its inventory directly impacts the Company's results of operations. The Company's inventories primarily consist of drugs it manufactures for its partners under contractual terms. Isis' inventories are stated at the lower of cost or market, cost being determined under the first-in, first-out method. Isis reviews inventories periodically and reduces items considered to be slow moving or obsolete to estimated net realizable value through an appropriate reserve. If the Company's estimates of the market value of its inventories are more favorable than actual market conditions, the Company may be required to make inventory write-downs in the future. There was no inventory as of

December 31, 2001. Inventory includes the following categories as of December 31, 2002, net of reserves (in thousands):

	December 31, 2002
Raw materials	$ 10,186
Work-in-process	904
Finished goods	—
	$ 11,090

Property, plant and equipment

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

	December 31,	
	2002	2001
Land	$ 1,163	$ 1,163
Buildings and improvements	37,870	23,852
Equipment	58,274	36,078
Furniture and fixtures	2,224	1,604
	99,531	62,697
Less accumulated depreciation	(40,437)	(34,452)
	$ 59,094	$ 28,245

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

Building	31.5 years
Building improvements	15 years
Manufacturing facilities	10 years
Leasehold improvements	10 years
Equipment	3 - 5 years
Furniture and fixtures	5 years

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. The license from Hybridon comprises the majority of the license balance as of December 31, 2002 and 2001. Isis amortizes licenses capitalized over their estimated useful life or term of the agreement, which for current licenses is between six years and 15 years. Accumulated amortization related to licenses was $2.5 million and $1.4 million at December 31, 2002 and 2001, respectively.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. 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 for impairment and are 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 7.0 years and 6.7 years at December 31, 2002 and 2001,

respectively. Accumulated amortization related to patents was $3.2 million and $2.3 million at December 31, 2002 and 2001, respectively.

Investment in affiliates

Isis uses the equity method of accounting to account for its investments in 50% or less owned companies over which it has the ability to exercise significant influence. Isis also accounts for investments in its joint ventures, Orasense and HepaSense, using the equity method of accounting. At December 31, 2002 and 2001, 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 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, throughout the respective terms of the collaborations related to the joint ventures, Elan and its subsidiaries retained significant minority investor rights that were considered "participating rights" as defined in Emerging Issues Task Force (EITF) No. 96-16. Accordingly, Isis accounted for its investment in each joint venture under the equity method of accounting. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. See Note 6—Research and Development Collaborative Arrangements and Licensing Agreements for more detail on the Company's investment in Orasense and HepaSense.

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, 2002.

Long-lived assets

In August 2001, the Financial Accounting Standards Board (FASB) issued SFAS 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 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 (APB) 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 adoption of this new standard has not had 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 issued 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 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 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. As of December 31, 2002, all of these options were either exercised or expired.

Stock-Based Employee Compensation

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

	2002	2001	2000
Net loss—as reported	$ (73,302)	$ (75,131)	$ (54,699)
Net loss—pro forma	$ (95,170)	$ (82,598)	$ (63,110)
Basic net loss per share—as reported	$ (1.35)	$ (1.70)	$ (1.48)
Basic net loss per share—pro forma	$ (1.75)	$ (1.87)	$ (1.71)

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 2002: a risk-free interest rate of 3.8%; a dividend yield of 0%; a volatility factor of 78.7% and an option life of 5.4 years; 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; and for 2000: a risk-free interest rate of 6.0%; a dividend yield of 0%; a volatility factor of 80.0% and an option life of 4.2 years. The weighted average fair value of options granted was $11.34 for 2002, $12.14 for 2001, and $7.81 for 2000.

Comprehensive income (loss)

SFAS 130, *Reporting Comprehensive Income* (SFAS 130) requires Isis to display comprehensive income (loss) and its components as part of Isis' full set of 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, 2002, 2001 and 2000 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 April 2002, the FASB issued SFAS 145, *Rescission of FASB Statements No. 4, 44, and 64, Amendment of FASB Statement No. 13, and Technical Corrections.* SFAS 4 required all gains or losses from extinguishment of debt to be classified as extraordinary items net of income taxes. SFAS 145 requires that gains and losses from extinguishment of debt be evaluated under the provisions of APB Opinion 30, and be classified as ordinary items unless they meet the specific criteria for treatment as an extraordinary item. The Company adopted the provisions of SFAS 145 effective January 1, 2002, and applied them to its prepayment in May 2002 of the Company's 14% Senior Subordinated Notes and in July 2002 to the Company's prepayment of its 12% convertible debt. The prepayment of both the 14% and 12% debt did not meet the specific criteria prescribed by SFAS 145 to be considered an extraordinary item and as such was recorded as a component of net loss.

In June 2002, the FASB issued SFAS 146, *Accounting for Costs Associated with Exit or Disposal Activities*. SFAS 146 addresses financial accounting and reporting for costs associated with exit or disposal activities and nullifies EITF 94-3, *Liability Recognition for Certain Employee Termination Benefits and Other Costs to Exit an Activity (including Certain Costs Incurred in a Restructuring)*. Isis does not expect the adoption of SFAS 146 to have a material effect on its financial condition or results of operations. The principal difference between SFAS 146 and EITF 94-3 relates to the requirements under SFAS 146 for recognition of a liability for a cost associated with an exit or disposal activity. SFAS 146 requires that a liability for a cost associated with an exit or disposal activity be recognized when the liability is incurred. Under EITF 94-3, a liability for an exit cost as generally defined in EITF 94-3 was recognized at the date of an entity's commitment to an exit plan. The provisions of SFAS 146 are effective for exit or disposal activities that are initiated after December 31, 2002, with early application encouraged. We do not expect that the adoption of SFAS 146 will have a material impact on the Company's financial statements.

In December 2002, the FASB issued SFAS 148, *Accounting for Stock-Based Compensation—Transition and Disclosure*, an amendment of SFAS 123. This statement amends SFAS 123, *Accounting for Stock Based Compensation* to provide alternative methods of voluntarily transitioning to the fair value based method of accounting for stock-based employee compensation. SFAS 148 also amends the disclosure requirements of SFAS 123 to require disclosure of the method used to account for stock-based employee compensation and the effect of the method on reported results in both annual and interim financial statements. The disclosure provisions are effective for the year ended December 31, 2002. The Company has not yet completed the final evaluation of the transitioning options presented by SFAS 148. However, during 2003, we expect to reach a determination of whether and, if so when, to change our existing accounting for stock-based compensation to the fair value method in accordance with the transition alternatives of SFAS 148.

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 maximize trends in yields and interest rates without compromising safety and liquidity. Isis has not experienced any material losses on its short-term investments.

As of December 31, 2002, 45%, 52% and 3% of the debt securities held by Isis had a contractual maturity of one year or less, one year to three years, and three years to 4.5 years, respectively.

Isis has obtained an ownership interest of less than 20% in two public companies it conducts business with, Antisense Therapeutics Limited (ATL) and Hybridon. In determining if and when a decrease in market value below the company's cost is other-than-temporary in its equity positions, Isis examines historical trends in stock price, the financial condition and near term prospects of the issuer,

and Isis' current need for cash. When a decline in value is deemed to be other-than-temporary, the Company recognizes an impairment loss in the period operating results to the extent of the decline. To date, Isis has not experienced any impairment losses related to these investments.

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, 2002			
U.S. Treasury securities and obligations of U.S. Government agencies	$ 89,607	$ 758	$ 90,365
U.S. corporate debt securities	96,202	930	97,132
Corporate equity securities	5,045	(2,296)	2,749
Total	$ 190,854	$ (608)	$ 190,246
Less current portion included in short-term investments	185,809	1,688	187,497
Less current portion included in other current assets	4,475	(2,296)	2,179
Non-current portion included in long-term investments	$ 570	$ —	$ 570

	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 included in short-term investments	$ 185,317	$ (310)	$ 185,007
Non-current portion included in long-term investments	$ 3,329	$ 970	$ 4,299

3. Long-Term Obligations and Commitments

In December 2002, Isis secured a $6.7 million term loan from a bank to refinance two existing notes. The note is secured by Isis' real property and bears interest at the prime interest rate, 4.25% at December 31, 2002, plus 0.5%. The loan requires monthly principal payments plus accrued interest with the remaining principal balance due in December 2006. The carrying value of this variable rate long-term note at December 31, 2002 was $5.7 million, 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 were secured by Isis' real property and bore interest at the prime interest rate of 4.75% at December 31, 2001, plus 0.5%. The balance of the two notes at December 31, 2001 was $6.3 million.

In September 2002, Isis agreed to manufacture Affinitak during the product launch period for Lilly. The agreement provides Isis with a loan of $21.0 million from Lilly to fund the construction of a new manufacturing suite dedicated to Affinitak. The interest rate is consistent with market conditions for similar credit facilities in place at the time the loan was agreed to. The loan is secured with the movable equipment purchased for the manufacturing suite. Isis will repay Lilly from Affinitak success

milestones due from Lilly, if we achieve such milestones, or other product-related cash flows. As of December 31, 2002, the balance on this loan was $15.4 million, which approximated fair value.

In May 2002, Isis completed a convertible debt offering of $125.0 million of 5 1/2% convertible subordinated notes due May 2009, which raised approximately $120.9 million, net of $4.1 million in issuance costs. Issuance costs are included in the balance sheet under Deposits and Other Assets and are being amortized over the life of the 5 1/2% notes. Interest on these notes is payable on a semi-annual basis. The notes are convertible by its holders into shares of common stock at a conversion price of $16.625 per share. Isis used a portion of the proceeds to prepay its 14% Senior Subordinated Notes, the obligations to Elan related to HepaSense and certain obligations to Elan related to Orasense. At December 31, 2002, the principal and accrued interest balance on this debt was $126.1 million, which approximated fair value.

In May 2002, the Company prepaid its 14% Senior Subordinated Notes, which were acquired between 1997 and 1998, using the proceeds from the issuance of the 5 1/2% convertible subordinated notes due May 2009. The prepayment of the debt consisted of $40.0 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt, which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. In connection with these notes, Isis issued to the lender warrants to purchase a total of 800,000 shares of Isis' common stock. The warrants expire on November 1, 2004 and are exercisable at $25 per share. The estimated fair value of the warrants using the Black-Scholes option pricing model was $5.4 million, based on 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 created a debt discount, which was amortized using the effective interest method. The effective interest rate of this debt was approximately 16%. The debt was carried on the balance sheet net of the unamortized debt discount and included accrued interest. The fair value of this debt at December 31, 2001 was $68.2 million and there was no balance for this debt at December 31, 2002.

In August 2001, Lilly made available to Isis a $100.0 million loan, to fund 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 drawdowns by Isis. As of December 31, 2002, the Company had drawn down $47.5 million of the $100.0 million available. The Company is accounting for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan was agreed to. The Company carries the net present value of its drawdowns as a long-term obligation and records interest expense over the term of the loan. The difference between the cash received and the present value of the loan represents value given to Isis by Lilly to help fund the research collaboration, and Isis is accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance. At December 31, 2002 and 2001, the balance in long-term obligations was $28.0 million and $9.7 million, respectively, and the balance in deferred revenue was $19.5 million and $10.3 million, respectively.

In January 2000, in conjunction with the HepaSense joint venture, Elan made available to Isis a $12.0 million line of credit evidenced by a convertible promissory note. The terms of the convertible promissory note provided for interest at 12% per annum, compounded semi-annually, maturing January 14, 2006. No principal or interest payments were required until the end of the loan. During 2002 and 2001, Isis borrowed $2.8 million and $2.6 million, respectively, under this convertible promissory note to provide development funding to HepaSense. Isis was able to prepay the loan 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 prepayment; provided that no more than 50% of any prepayment could be paid in Isis' common stock. In July 2002, Isis prepaid $7.9 million outstanding on this debt, which included accrued interest, using the proceeds from the 5 1/2% convertible subordinated notes. As of December 31, 2002,

---

the HepaSense convertible promissory note was fully paid and Isis cannot borrow any additional funds against it.

In September 1999, Isis borrowed $1.0 million from Abbott for use by Isis as Isis' contribution toward costs associated with Abbott's design and construction of a facility for commercial scale manufacturing of oligonucleotides. The debt had an annual interest rate of 2% over the Citibank prime rate calculated annually from the date of borrowing and the interest was payable annually. The interest rate on this debt was 6.75% and 8.5% at December 31, 2002 and 2001, respectively. The balance under this borrowing facility as of December 31, 2002 and 2001 was $1.0 million, which approximated fair value. Isis repaid the principal of $1.0 million and accrued interest of $21,000 in cash in January 2003.

In April 1999, in conjunction with the Orasense joint venture, Elan made available to Isis an $18.4 million line of credit evidenced by a convertible promissory note. The terms of the convertible promissory note provide for 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. During 2002 and 2001, Isis borrowed $919,000 and $5.6 million, respectively, under this convertible promissory note to provide development funding to Orasense. 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, Elan may convert all or any portion of the loan outstanding, on a per tranche basis, into the number of shares of Isis 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 was subordinate to the $40.0 million private debt financing, which was prepaid in May 2002. In July 2002, Isis prepaid $11.8 million of the outstanding balance, including accrued interest, on the Orasense convertible promissory note, using the proceeds from the 5 1/2% convertible subordinated notes. Based on the principal and accrued interest outstanding at December 31, 2002, the loan balance due at maturity will be $9.4 million, provided that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility, including accrued interest, as of December 31, 2002 and 2001 was $7.2 million and $16.7 million, respectively, which approximated fair value. Isis cannot borrow any additional principal under the Orasense promissory note.

In 1996 and 1997, Isis borrowed a total of $22.6 million under a $40.0 million 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, 2002 and 2001 was $22.6 million, which approximated fair value.

Annual debt maturities at December 31, 2002 are as follows (in thousands):

2003	$ 17,834
2004	7,055
2005	35,888
2006	4,898
2007	40

Thereafter	140,354
Total	$ 206,069

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, 2002 are as follows (in thousands):

	Operating Leases	Capital Leases
2003	$ 2,505	$ 4,191
2004	2,347	3,195
2005	2,081	1,815
2006	2,146	—
2007	1,626	—
Thereafter	3,679	—
Total minimum payments	$ 14,384	$ 9,201
Less amount representing interest		(942)
Present value of future minimum payments		$ 8,259
Less current portion		(3,602)
Long-term portion		$ 4,657

Rent expense for the years ended December 31, 2002, 2001, and 2000 was $2.9 million, $2.3 million, and $2.1 million, respectively. Cost of equipment under capital leases at December 31, 2002 and 2001 was $18.7 million and $13.0 million, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2002 and 2001 was approximately $10.3 million and $7.6 million, respectively.

4. Stockholders' Equity

Preferred Stock

The Company is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2002, outstanding preferred stock consists of 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

In August 2002, the holder of the Company's Series A Convertible Exchangeable Preferred Stock exercised its option to convert the Series A shares into Isis common stock. The transaction converted the outstanding 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of Isis common stock using a conversion price of $21.54 per share. Included in the conversion were approximately $2.1 million in preferred stock dividends accrued in prior periods. At December 31, 2001, Isis had 120,150 shares authorized, issued and outstanding of Series A Convertible 5% Preferred Stock.

Series B Convertible Exchangeable 5% Preferred Stock

At December 31, 2002, 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 at $14.00 per share, which is 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to June 30, 2002. In the event of a significant transaction, the shares are convertible into Isis' common stock at 125% of the average closing price of Isis' common stock for the 60 trading days ending two business days prior to the significant transaction. 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

In April 2002, Isis achieved a $3.8 million development milestone in its HepaSense Ltd. joint venture with Elan and as a result, issued 126,093 shares of Isis common stock to Elan at a price of $29.74 per share. The number of shares was determined by dividing the $3.8 million by 140% of the average closing price of the common stock for the 60 trading days ending two days prior to the milestone being achieved.

In August 2002, the holder of Isis' Series A Convertible Preferred Stock exercised its option to convert the Series A shares into Isis common stock. The transaction converted the outstanding 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of Isis common stock using a conversion price of $21.54 per share. Included in the conversion were approximately $2.1 million in preferred stock dividends accrued in prior periods. At December 31, 2001, Isis had 120,150 shares authorized, issued and outstanding of Series A Convertible 5% Preferred Stock.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis adopted a stock option plan that 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, 2002, a total of 4,949,000 options were outstanding, options to purchase 4,032,000 shares were exercisable, and 566,000 shares were available for future grant.

2000 Broad-Based Equity Incentive Plan

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of

Directors increased the 2000 Plan by 2,000,000 shares, allowing for the purchase of up to 5,990,000 shares of common stock by 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. At December 31, 2002, a total of 4,014,000 options were outstanding, 1,258,000 shares were exercisable, and 1,723,000 shares were available for future grant.

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, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 803,000 shares of common stock reserved for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2002, a total of 293,000 options were outstanding, 142,500 of the shares issued under this plan were exercisable and 510,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 2000 through December 31, 2002 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
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
Granted	2,197	$ 6.87 to $22.19	
Exercised	(505)	$ 4.00 to $17.88	
Terminated	(656)	$ 5.38 to $24.17	
Outstanding at December 31, 2002	9,256	$ 3.75 to $26.65	$ 11.34

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 12/31/02	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/02	Weighted Average Exercise Price
$3.75 - $5.88	388	1.96	$ 4.28	388	$ 4.28
$6.00 - $6.88	2,273	5.85	$ 6.74	1,833	$ 6.72
$7.00 - $8.88	624	7.99	$ 8.02	169	$ 7.72
$9.00 - $9.94	1,138	7.92	$ 9.57	510	$ 9.58
$10.00 - $10.94	628	7.24	$ 10.35	385	$ 10.33
$11.00 - $11.99	417	8.00	$ 11.40	171	$ 11.47
$12.00 - $12.94	1,479	5.94	$ 12.49	1,220	$ 12.55
$13.00 - $14.98	454	4.48	$ 13.54	411	$ 13.46
$15.00 - $17.88	531	8.26	$ 16.45	132	$ 16.05
$18.00 - $19.89	222	5.58	$ 18.19	163	$ 18.10
$20.00 - $26.65	1,102	8.98	$ 21.29	50	$ 22.02
$3.75 - $26.65	9,256	6.73	$ 11.34	5,432	$ 9.78

Employee Stock Purchase Plan

In 2000, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan and reserved 200,000 shares of common stock for issuance thereunder. In both 2001 and 2002, an additional 200,000 shares of common stock were reserved for the 2000 Employee Stock Purchase Plan, resulting in a total of 600,000 shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. During 2002, 178,000 shares were issued under this plan to employees at prices ranging from $6.93 to $10.20 per share. At December 31, 2002, 307,000 shares were available for purchase under this plan.

Warrants

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

In 2000, Isis issued warrants to purchase 14,881 shares of common stock to Elan as part of the joint venture collaboration between Isis and Elan to form HepaSense. As of December 31, 2002, all of the warrants remained outstanding at an exercise price of $50.40 per share. The warrants expire May 1, 2008.

In 1999, Isis issued warrants to purchase 215,000 shares of common stock to Elan as part of the joint venture collaboration between Isis and Elan to form Orasense. As of December 31, 2002, all of the warrants remained outstanding at an exercise price of $24 per share. The warrants expire April 19, 2004.

In 1997 and 1998, Isis issued warrants to purchase 500,000 and 300,000 shares of common stock, respectively, in conjunction with a private debt financing agreement. As of December 31, 2002, all of the warrants remain outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3.

As of December 31, 2002, total common shares reserved for future issuance was approximately 13,399,000.

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2002 and 2001 are shown below (in thousands). Valuation allowances of $197.3 million and $169.0 million have been recognized for 2002 and 2001, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2002	2001
Deferred tax assets:		
Capitalized research expense	$ 17,780	$ 6,685
Net operating loss carryforwards	135,688	111,514
Research and development credits	24,634	29,572
Deferred revenue	19,573	18,047
Other, net	617	4,305
Total deferred tax assets	198,292	170,123
Deferred tax liabilities:		
Intangible Assets	(921)	(1,091)
Total deferred tax liabilities	(921)	(1,091)
Total net deferred tax assets	197,371	169,032
Valuation allowance for deferred tax assets	(197,371)	(169,032)

Net deferred tax assets	$ —	$ —

At December 31, 2002, approximately $7.2 million 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, 2002, Isis had federal and California tax net operating loss carryforwards of approximately $381.1 million and $40.1 million, respectively. Isis also had federal and California research credit carryforwards of approximately $17.7 million and $8.8 million, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of California loss carryforwards. The federal tax loss carryforwards and the research credit carryforwards will begin expiring in 2004 unless previously utilized. The California tax loss carryforwards will begin expiring in 2004, unless utilized.

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

6. Research and Development Collaborative Arrangements and Licensing Agreements

Drug Discovery, Development and Commercialization Collaborations

In December 2001, Isis licensed to ATL, an Australian company publicly traded on the Australian Stock Exchange, ISIS 107248 (ATL 1102), 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. As part of the collaboration, ATL pays Isis research

fees and may purchase drug from Isis. Under the terms of the agreement and upon the completion of ATL's initial public offering in December 2001, Isis received 14% of ATL's common stock. Upon completion of ATL's IPO, Isis received 30,000,000 common shares and options for 20,000,000 additional common shares. Isis valued its 14% ownership at $2.8 million based on ATL's IPO price and is recognizing the amount as revenue over the term of the agreement. In December 2002, ATL successfully completed a subsequent share placement, in which Isis participated as an investor. As of December 31, 2002, Isis owned approximately 15% of ATL's equity, which Isis accounted for as a short-term investment. For the years ended December 31, 2002 and 2001, Isis recorded revenue in the statement of operations as research and development revenue under collaborative agreements of $3.7 million and $46,000, respectively.

In December 2001, Isis initiated a three-year research collaboration with Amgen Inc. (Amgen) to discover new antisense drugs. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration. The collaboration provided Isis with an upfront fee and provides Isis annual research support. 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. For the years ended December 31, 2002 and 2001, Isis recorded $3.6 million and $250,000, respectively, from this collaboration which is included in the statement of operations as research and development revenue under collaborative agreements. The 2002 revenue of $3.6 million included a milestone payment Isis earned in 2002.

In November 2001, Isis established a drug development collaboration with OncoGenex Technologies Inc. (OncoGenex), 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 Isis' proprietary second-generation antisense chemistry. Pursuant to the agreement, Isis conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. Isis also manufactured OGX-011 for preclinical and Phase I/II studies. OncoGenex has responsibility to perform Phase I clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and to perform Phase I/II clinical trials in combination with standard chemotherapy in patients with solid tumors known to express clusterin including lung, prostate, renal, bladder and ovarian cancers. Revenue from this collaboration was included in the statement of operations as research and development revenue under collaborative agreements.

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

- Lilly purchased $75 million of Isis' common stock, 4,166,667 shares, at $18 per share.

- Isis licensed to Lilly rights to Affinitak (formerly LY90003), Isis' antisense drug in Phase III trials for the treatment of non-small cell lung cancer. Lilly paid Isis $25 million in upfront fees for Affinitak and agreed to reimburse Isis for its remaining Affinitak development and registration costs. For the years ended December 31, 2002 and 2001, Isis recorded revenue of $31.9 million and $9.2 million, respectively, related to reimbursement of Affinitak development costs. This revenue was included in the statement of operations as research and development revenue under collaborative agreements. The associated expenses were included in Isis' statement of operations as research and development expenses.

- Isis 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. In 2002, this collaboration was expanded to include oncology and the license of ISIS 23722.

- Lilly committed to lend Isis, interest-free, up to $100.0 million over a four-year period to fund its obligations under the drug discovery collaboration. This loan is repayable at the end of the four-year term in either cash or Isis common stock, at a fixed conversion price of $40 per share at Isis' option. During the years ended December 31, 2002 and 2001, Isis recorded revenue of $3.5 million and $407,000, respectively, related to the drug discovery collaboration. This revenue was included in the statement of operations as research and development revenue under collaborative agreements.

In September 2002, Isis further expanded its relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement Isis upgraded and expanded its manufacturing facility. Isis added a new state-of-the-art manufacturing suite dedicated to Affinitak. Lilly provided Isis with funding in the form of a loan of up to $21 million, to build the Affinitak suite. Isis will repay the loan from Affinitak success milestones due from Lilly, if Isis achieves such milestones, or other product-related cash flows. The movable equipment purchased for the manufacturing suite secures this loan. In February 2003, Isis completed construction of the facility, which is located on its Carlsbad campus in an existing building.

In May 2001, Isis agreed to license to Merck & Co, Inc. (Merck) its preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. In exchange for the license, Isis received an upfront payment In addition, Isis received development funding and a development milestone. For the years ended December 31, 2002 and 2001, Isis recorded revenue of $840,000 and $4.4 million, respectively, which was included in the statement of operations as research and development revenue under collaborative agreements. Isis reacquired full product rights to ISIS 113715 from Merck in December 2002.

In January 2000, Isis and Elan formed a joint venture, HepaSense, to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus, or HCV. In conjunction with this transaction, Isis sold 297,619 shares of Isis' common stock to Elan International Services, or EIS, for $7.5 million, 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 $12.0 million (See Note 4). In April 2002, Isis achieved a development milestone in HepaSense that triggered a $3.8 million equity purchase by Elan of Isis common stock at a price of $29.74. Elan also received a warrant to purchase 6,304 shares of Isis common stock at an exercise price of $59.48 per share. The result of this transaction increased Isis' cash balance and was not recorded as revenue. Isis and Elan provided development and manufacturing services to HepaSense during the joint venture. For the years ended December 31, 2002, 2001 and 2000 Isis recorded revenue of $3.0 million, $5.2 million and $2.8 million, respectively, from HepaSense, which were included in the statement of operations as research and development revenue from affiliates. For the years ended December 31, 2002, 2001, and 2000, Isis recorded $6.5 million, $8.3 million, and $6.2 million, respectively, as equity in the loss of HepaSense. Additionally, at December 31, 2001, the balance sheet included $2.5 million of contracts receivable relating to HepaSense. There was no contracts receivable relating to HepaSense at December 31, 2002. In November 2002, Elan concluded its participation in the HepaSense collaboration in conjunction with its continuing restructuring efforts. As a result, Isis regained all rights to ISIS 14803, with a potential nominal royalty due to HepaSense. HepaSense will distribute the royalty to Elan and Isis on a pro rata basis based on each parties quity ownership in HepaSense. This favorable outcome allows Isis to pursue the clinical development of ISIS 14803.

In April 1999, Isis and Elan formed a joint venture, Orasense, to develop technology for the formulation of oral oligonucleotide drugs. In conjunction with the formation of the Orasense joint venture, Isis sold 910,844 shares of Isis' common stock to EIS, for $15.0 million, and issued EIS 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 $12.0 million (See Note 4). For the years ended December 31, 2002, 2001 and 2000, Isis recorded revenue of $8.9 million, $5.4 million and $5.2 million, respectively, from Orasense, which were included

in the statement of operations as research and development revenues from affiliates. For the years ended December 31, 2002, 2001 and 2000, Isis recorded $9.5 million, $10.3 million and $9.7 million, respectively, as equity in the loss of Orasense. Additionally, at December 31, 2002 and 2001, the balance sheet included $6.2 million and $1.7 million, respectively, of contracts receivable relating to Orasense. Also, as of December 31, 2002, Isis had a funding obligation due to Orasense of $5.2 million. Isis intends to fully fund Orasense for this obligation in 2003. The original research agreement and funding period for Orasense ended in July 2002. In 2002, Elan and Isis agreed to extend the Orasense collaboration. Effective December 31, 2002 Elan concluded its participation in the Orasense collaboration in conjunction with its continuing restructuring efforts. As a result, Isis has regained all rights to ISIS 104838, with a potential royalty due to Orasense. Orasense will distribute the royalty to Elan based on Elan's equity ownership in Orasense.

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 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 2001, Pantheco issued additional shares and Isis' holdings in Pantheco declined to 15.5% and Isis currently holds 15.5% of Pantheco's outstanding shares. For the year ended December 31, 2000, Isis recorded $1.1 million as licensing revenue, which reflected the value of Pantheco's common stock that Isis received in exchange for the second license of Isis' PNA chemistry. For the years ended December 31, 2001 and 2000, Isis recorded $267,000 and $285,000, respectively, under equity in loss of affiliates. Isis used the equity method of accounting for its holdings of Pantheco during the periods of 2001 and 2000 when Isis' holdings were in excess of 20%. There was no equity in loss of affiliates for 2002 as Isis' accounted for its investment in Pantheco on a cost basis in 2002.

In June 1998, Isis entered into a research collaboration with Merck to discover small molecule drug candidates to treat patients infected with HCV. In April 2002, Isis and Merck extended this research collaboration for an additional year. Within the collaboration, Isis and Merck design, synthesize, and evaluate novel compounds that Merck screens 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. 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 revenue under collaborative agreements for the years ended December 31, 2002, 2001 and 2000, is revenue of $2.2 million, $3.6 million and $3.0 million, respectively, from Merck under the terms of this agreement.

In July 1997, Isis and Novartis Ophthalmics AG (Novartis), formerly CIBA Vision Corporation, entered into an agreement granting Novartis exclusive worldwide distribution rights for Vitravene (fomivirsen). Under the terms of the agreement, Isis manufactures and sells Vitravene to Novartis, who is responsible for worldwide sales and marketing. Included in the statement of operations as research and development revenue under collaborative agreements for the years ended December 31, 2002 and 2000, is revenue related to the shipment of Vitravene of $293,000 and $274,000, respectively. There was no revenue related to the shipment of Vitravene for the year ended December 31, 2001. Isis also earned a $2.5 million milestone payment in each year, 2001 and 2000. Each milestone was included in the statement of operations as research and development revenue under collaborative agreements.

GeneTrove Collaborations

Isis' GeneTrove division has partnerships with major pharmaceutical and biotechnology companies in which Isis provides one or more of the following services:

- Gene functionalization and/or target validation services to help Isis' partners validate and prioritize genes for their drug discovery programs,
- Access to Isis' inhibitor library,
- A license to specific intellectual property that a partner may use in its in-house functional genomics programs and/or for its customers

Revenue from these partnerships was included in the statement of operations as research and development revenue under collaborative agreements. Isis' partners in 2002 included:

- Abbott Laboratories
- Amgen
- atugen AG
- Aventis
- Celera
- Chiron Corporation
- GlaxoSmithKline plc.
- Johnson & Johnson Pharmaceutical Research & Development, LLC.
- Merck
- Pfizer
- Pharmacia Corporation

Isis recently extended GeneTrove's collaboration with Celera to end in June 2003. GeneTrove's collaborations with Abbott and Aventis concluded in 2002 under the terms of their agreements.

Ibis Therapeutics Collaborations

Since its inception, Ibis has received significant financial support from various government agencies to use its technology to develop broad-spectrum anti-infective drugs that Isis believes will have usefulness in national defense. In early 2002, Ibis received a three-year contract to continue its drug discovery program with the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. The contract provides for funding of up to $2.4 million. Ibis is continuing its work with government agencies by applying its technology to develop a sensor to detect infectious agents that could be used in biological warfare attacks in a program called Triangulation Identification Genetic Evaluation of biological Risks, or TIGER. Ibis is collaborating with San Diego-based Science Applications International Corporation, or SAIC, on this multi-year program funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $9.8 million for its efforts related to TIGER. Ibis also has research relationships with several other government entities including the United States Navy, the Federal Bureau of Investigations and the Center for Disease Control and Prevention. For the years ended December 31, 2002, 2001, and 2000, Isis had revenue from government grants and contracts of $5.9 million, $2.9 million and $2.9 million, respectively, which Isis included in the statement of operations as research and development revenue under collaborative agreements.

In addition to the projects with government agencies, Ibis collaborated with Pfizer from June 2000 through June 2002 for the discovery and development of small molecule drugs against certain RNA targets. During this period, Ibis earned two research milestones totaling $4.0 million. This collaboration ended in June 2002 in accordance with its terms. For the years ended December 31, 2002, 2001 and 2000, Isis had revenue of $1.4 million, $7.3 million and $2.4 million, respectively, under this agreement, which the Company included in the statement of operations as research and development revenue under collaborative agreements.

Licensing Agreements

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc. (Eyetech), a privately held company, certain Isis patents necessary for Eyetech to develop, make and commercialize Macugen, formerly EYE001, a non-antisense compound intended for use in the treatment of ophthalmic diseases. Under the transaction, Eyetech paid Isis a $2.0 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 Macugen. Isis has no further obligations under the agreement. For the year ended December 31, 2001, Isis recorded revenue of $2.0 million, which was included in the statement of operations as licensing and royalty revenue.

In December 2001, Isis established a long-term research scale antisense inhibitor supply agreement with Integrated DNA Technologies, Inc. (IDT), which provides for IDT to manufacture research scale antisense inhibitors and research reagents to Isis' specifications. Isis paid IDT $5.0 million toward future purchases of supplies and expanded its existing licensing agreement on certain antisense patents to allow Isis to exclusively sublicense these patents for functional genomics purposes. The agreement also eliminated milestone payments and reduced royalty rates Isis was to pay IDT for commercialized second-generation antisense drugs. In addition, Isis paid IDT $350,000 and $3.5 million in 2002 and 2001, respectively, and will pay IDT $1.1 million over the next three years for the license. At December 31, 2002 and 2001, Isis' balance sheet reflected a deposit of $4.5 million and $5.0 million, respectively, and a licensing asset, net of amortization, of $4.5 million and $3.5 million, respectively.

In May 2001, Isis and Hybridon, Inc. (Hybridon) 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 RNaseH 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 Isis' stock price. In return for access to Isis' patents, Hybridon agreed to issue Isis $6.0 million in Hybridon common stock before May 2004 subject to acceleration tied to Hybridon's common stock price. In 2001, Isis issued 857,143 shares of common stock, valued at $15.0 million, in accordance with this agreement. In August 2002, Isis and Hybridon canceled the remaining reciprocal financial obligations related to this agreement. Under the original terms, Hybridon owed Isis an additional 4,000,000 shares of Hybridon common stock, due in 2002, and Isis owed Hybridon $4.5 million in cash or stock, due in May 2003. The cancellation of the obligations resulted in a decrease to Isis' carrying value of the license in the amount of $500,000. Isis' balance sheet at December 31, 2002 and 2001 reflected a licensing asset, net of amortization, of $25.1 million and $27.4 million, respectively, related to this agreement. At December 31, 2001, the net receivable from Hybridon was $1.5 million. There was no receivable from Hybridon or a payable to Hybridon at December 31, 2002.

7. Restructuring

In November 2002, Isis announced the termination of the GeneTrove database product offering and the resulting reorganization of the GeneTrove division. As a result, Isis reduced its workforce by

approximately 25 people. The restructuring plan also provided for the write-down of certain intellectual property. As a result of this plan, restructuring related charges of approximately $1.4 million were recognized as operating expenses in the fourth quarter of 2002.

The following table summarizes the balance of the accrued restructuring reserve, which has been included in accrued liabilities at December 31, 2002 (in thousands):

	Severance Cost for Involuntary Employee Terminations	Write-down of Intellectual Property	Total
Balance at December 31, 2001	$ —	$ —	$ —
Reserve established	768	605	1,373
Utilization of reserves:			
Cash	(379)	—	(379)
Non-cash	—	(605)	(605)
Balance at December 31, 2002	$ 389	$ —	$ 389

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 ($11,500 for 2002). Isis made approximately $413,000 and $295,000 in matching contributions for the years ended December 31, 2002 and 2001, respectively.

9. Affiliate Supplementary Disclosure

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in Orasense under the equity method of accounting. At inception, Elan granted to Orasense a license to its intellectual property for $15.0 million. The term of the license was 3 years and amortization expense related to this license was $1.3 million and $5.0 million for the years ended December 31, 2002 and 2001, respectively. Orasense has incurred research and development expenses, performed by Elan and Isis on Orasense's behalf, in the course of its product development. The original research agreement and funding period for Orasense ended in April 2002. In 2002, Isis and Elan agreed to amend the terms and extend their collaboration in this joint venture. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the Orasense collaboration

effective December 31, 2002. The following table presents summary financial information (in thousands, except per share amounts) for Orasense as of and for the years ended:

	December 31,	
Balance Sheet:	2002	2001
Assets		
Cash and cash equivalents	$ 9	$ 11
Licenses	—	1,250
Total assets	$ 9	$ 1,261

Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ 6,537	$ 2,097
Other current liabilities	—	—
Common stock, $1.00 par value; 12,000 authorized, issued and outstanding at December 31, 2002 and 2001	12	12
Additional paid-in capital	39,388	33,170
Accumulated deficit	(45,928)	(34,018)
Total liabilities and stockholders' equity	$ 9	$ 1,261

Results of Operations:

Revenues	$ —	$ —
Research and development expenses	10,660	7,864
Amortization of acquired license	1,250	5,000
Total operating expenses	11,910	12,864
Net loss	$ (11,910)	$ (12,864)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in HepaSense under the equity method of accounting. At inception, Elan granted to HepaSense a license to its intellectual property for $15.0 million. The term of the license was 3 years and amortization expense related to this license totaled $5.0 million for years ended December 31, 2002 and 2001. HepaSense has incurred research and development expenses, performed by Elan and Isis on HepaSense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the HepaSense collaboration and Isis

reacquired all rights to ISIS 14803. The following table presents summary financial information (in thousands, except per share amounts) for HepaSense as of and for the years ended:

	December 31,	
Balance Sheet:	**2002**	**2001**
Assets		
Cash and cash equivalents	$ 4	$ 4
Licenses	—	5,000
Total assets	$ 4	$ 5,004
Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ —	$ 2,551
Other current liabilities	—	—
Common stock, $1.00 par value; 6,001 shares authorized, issued and outstanding at December 31, 2002 and 2001	6	6
Series A Preferred stock, $1.00 par value; 6,000 shares authorized, issued and outstanding at December 31, 2002 and 2001	6	6
Additional paid-in capital	26,221	20,558
Accumulated deficit	(26,229)	(18,117)
Total liabilities and stockholders' equity	$ 4	$ 5,004

Results of Operations:

Revenues	$ —	$ —
Research and development expenses	3,112	5,317
Amortization of acquired license	5,000	5,000
Total operating expenses	8,112	10,317
Net loss	$ (8,112)	$ (10,317)

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, 2002, and 2001 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2002 Quarters				
Revenues	$ 17,959	$ 20,061	$ 20,300	$ 21,859
Operating expenses	27,677	32,400	37,809	33,106
Loss from operations	(9,718)	(12,339)	(17,509)	(11,247)
Net loss	(17,972)	(20,865)	(17,576)	(15,829)
Accretion of dividends on preferred stock	(335)	(335)	(222)	(168)
Net loss applicable to common stock	$ (18,307)	$ (21,200)	$ (17,798)	$ (15,997)
Basic and diluted net loss per share(1)	$ (0.34)	$ (0.39)	$ (0.33)	$ (0.29)

	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)

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

QuickLinks

QuickLinks -- Click here to rapidly navigate through this document

RESTATED 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 22, 2002. Capitalized terms not otherwise defined herein will have the meanings given to them in Exhibit A attached hereto.

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:

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.

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.

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.

(l) Unless a Seller's Sellers Plan explicitly instructs Broker to do otherwise, if Broker exercises an option because such Option was about to expire, Broker must sell the shares of Stock issued upon the exercise of such Option within 5 Trading Days of exercise at the then prevailing market price for the Stock, regardless of the Minimum Sales Prices set forth in the applicable Sellers Plan.

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.

General.

(f) 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.

(g) 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.

(h) 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.

(i) 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.

(j) 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.

(k) 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.

(l) 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.

(m) 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 Presiden

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 (i) the Nasdaq Stock Market is open for business and the Stock trades regularly on such day and (ii) Isis is open for business as a corporation.

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)

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

o Exercise first those Options with the lowest exercise price.

(Please Check Only One of The Following)

o 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

o 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:

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

o 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

o 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)***:**

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

o _____ shares of Stock; or

o 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

o _____ 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

- o 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:

Options:

Option Number	Number of Shares	Exercise Price	Expiration Date

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.

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

2. 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.

3. 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.

4. 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.

5. 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.

1. While the Sellers Plan is in effect, Seller agrees not to (i) buy or sell any securities of Isis outside of the transactions contemplated by the Trading Plan and purchases pursuant to Isis' Employee

Stock Purchase 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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

QuickLinks

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 10.53

AMENDMENT

This Amendment to the Collaborative Research and License Agreement dated July 9, 2001, ("Agreement"), by and between **ISIS PHARMACEUTICALS, INC.** ("Isis"), a Delaware corporation, with its principal office at 2292 Faraday Avenue, Carlsbad, California 92008 and **PE CORPORATION (NY),** a New York corporation, through the **CELERA GENOMICS GROUP**, ("Celera"), having a principal place of business at 45 West Gude Drive, Rockville, Maryland 20850. Celera and Isis may be referred to herein individually as a "Party" and collectively as the "Parties".

WHEREAS, Celera and Isis entered into the Agreement to collaborate to generate information on gene function for up to 250 gene targets; and

WHEREAS, Celera and Isis desire to amend the Agreement.

NOW, THEREFORE, in consideration of the mutual covenants and promises contained herein, the Parties agree to amend the Agreement as follows:

1. Section 1.4(a) is added as follows:

   1.4(a) "Celera Conditional Target" means a Gene selected by Celera and included by Isis in the HTGF queue under the conditions set forth in Section 3.1(b).

2. Section 3.1(b) is amended by adding the following:

   Upon approval by Celera, Isis will include a Gene in the HTGF queue notwithstanding the right of Isis under this Section to exclude such Gene provided that such Gene will not become: (i) part of the Celera Gene Availability Pool, or (ii) a Celera Exclusive Target (such Gene a "Celera Conditional Target"). Except as provided in the preceding sentence, all Celera Conditional Targets will be treated equally hereunder with any other Gene included in the HTGF queue. Isis will notify Celera in writing of the identity of any Gene which Isis would include in the HTGF queue only as a Celera Conditional Target within ten (10) business days of Celera's selection of such Gene. If Celera wishes to approve such Gene as a Celera Conditional Target, Celera will notify Isis in writing within fifteen (15) business days of receipt of Isis's notification, provided, however, that Isis will have no obligation to reserve such Gene for Celera prior to receiving notification of Celera's approval of such Gene as a Celera Conditional Target. If Celera does not approve such Gene as a Celera Conditional Target, such Gene will become a Rejected Gene.

This Amendment will be attached to the Agreement and incorporated therein. All other terms of the Agreement will remain in full force and effect.

PE CORPORATION (NY)

By: /s/ MARK D. ADAMS

Mark D. Adams, Ph.D.
Vice President, Genome Programs

Date: 4/19/02

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President

Date: 4/22/02

QuickLinks

Exhibit 10.53

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 10.54

AMENDMENT NO. 2

This Amendment No. 2 ("Amendment No. 2") to the Collaborative Research and License Agreement effective July 9, 2001 ("Agreement") is made by and between **ISIS PHARMACEUTICALS, INC.** ("Isis"), a Delaware corporation, with its principal office at 2292 Faraday Avenue, Carlsbad, California 92008 and **APPLERA CORPORATION,** a Delaware corporation, through the **CELERA GENOMICS GROUP**, ("Celera"), having a principal place of business at 45 West Gude Drive, Rockville, Maryland 20850. Celera and Isis may be referred to herein individually as a "Party" and collectively as the "Parties." This Amendment shall be effective as of the date of last signature below by an authorized representative of the Parties.

WHEREAS, PE Corporation (NY) through the Celera Genomics Group and Isis entered into the Agreement effective July 9, 2001 to collaborate to generate information on gene function for up to two-hundred fifty (250) gene targets;

WHEREAS, PE Corporation (NY) has been liquidated and all of its assets, subject to all of its liabilities, have been transferred to Applera Corporation as of July 1, 2002, and, in accordance with Section 12.2 of the Agreement, the Agreement, and Amendment No. 1 dated April 22, 2002 shall be binding upon Applera Corporation and shall be deemed to include the name of Applera Corporation to the extent necessary to carry out the intent of the Agreement and Amendment No. 1 together with this Amendment No. 2.

WHEREAS, Celera and Isis desire to amend the Agreement to extend the Research Term.

NOW, THEREFORE, in consideration of the mutual covenants and promises contained herein, the Parties agree to amend the Agreement as follows:

1. Section 1.40, Research Term is hereby deleted and replaced with language that reads as follows:

   "Research Term" means the period commencing on the Effective Date and terminating twenty three (23) months thereafter (or such earlier date as of which this Agreement is terminated hereunder).

2. This Amendment will be attached to the Agreement and incorporated therein. All other terms of the Agreement will remain in full force and effect.

APPLERA CORPORATION
Through the Celera Genomics Group

By: /s/ MARK D. ADAMS, PH.D.

Name: Mark D. Adams, Ph.D.
Title: Vice President, Genome Programs

Date: January 15, 2003

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

Name: B. Lynne Parshall
Title: Executive Vice President

Date: January 22, 2003

QuickLinks

Exhibit 10.54

QuickLinks -- Click here to rapidly navigate through this document

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

QuickLinks

Exhibit 21.1

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Forms S-8 and Forms S-3) of Isis Pharmaceuticals, Inc. of our report dated January 30, 2003 with respect to the financial statements of Isis Pharmaceuticals, Inc. included in the Annual Report (Form 10-K) for the year ended December 31, 2002.

/s/ ERNST & YOUNG

San Diego, California
March 26, 2003

QuickLinks

Exhibit 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 99.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2002, to which this Certification is attached as Exhibit 99.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: March 31, 2003

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	B. Lynne Parshall, Esq. Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

QuickLinks