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, 2000
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 and Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes X No .
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Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. Yes X No .
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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 $299,046,755 as of January 12, 2001.*

The number of shares of voting common stock outstanding as of January12, 2001 was 40,119,564.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Registrant's definitive Proxy Statement filed on or about February 28, 2001 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on April 6, 2001 is incorporated by reference into Part III of this Report.

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*Excludes 10,584,082 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 January 12, 2001. 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 THE COMPANY'S BUSINESS AND THE THERAPEUTIC AND COMMERCIAL POTENTIAL OF ITS TECHNOLOGIES AND PRODUCTS IN DEVELOPMENT. 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, AND THE ENDEAVOR OF BUILDING A BUSINESS AROUND SUCH POTENTIAL PRODUCTS. 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, THE READER IS CAUTIONED NOT TO RELY ON THESE FORWARD-LOOKING STATEMENTS.

PART I

ITEM 1. BUSINESS

OVERVIEW

The sequencing of the human genome is opening up significant new opportunities for the treatment of disease. At Isis, we are pioneering genomics-based drug discovery and development focused on RNA. RNA, or ribonucleic acid, contains all of the information the cell needs to produce proteins. Interaction with RNA can keep disease-causing proteins from being produced. Our goal is to discover and develop novel drugs to treat patients and to use our proprietary technologies to allow our pharmaceutical company partners to most efficiently capitalize on the opportunities provided by the genomics revolution. RNA is a novel target for drug discovery, and we believe we have established a dominant position in exploiting RNA as a drug target.

We have integrated our expertise in molecular and cellular biology, medicinal chemistry, RNA biochemistry, bioinformatics, pharmacology and clinical development to create two exciting technologies. Antisense, our leading technology, directly uses gene sequencing information to rationally design drugs. From this technology, we have put one product on the market and built a robust pipeline of eleven products in development, of which six products are in late stage clinical trials, either Phase II or Phase III. We have successfully leveraged our antisense technology through corporate collaborations with Elan Pharmaceuticals, Inc., Merck & Co., Inc.; AstraZeneca plc; Abbott Laboratories, Inc.; Aventis S.A., formerly Rhone-Poulenc Rorer; R.W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies; Novartis Ophthalmics, formerly CIBA Vision; Novartis AG and Boehringer Ingelheim International GmbH. These collaborations increase our financial resources, improve our technological strength and establish valuable development and commercial relationships.

Our Ibis Therapeutics-TM- division has created a complementary technology based on designing small molecule drugs that work by binding to structured RNA targets that are critical in disease processes. In 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a Pfizer company, in a research partnership worth up to $37 million.

Our GeneTrove-TM- division uses our antisense technology as a tool to provide pharmaceutical companies with vital information about genes that these companies are interested in targeting for drug discovery. We provide this information rapidly and efficiently, using the proprietary methods and systems that we developed to create antisense inhibitors as drugs. We have collaborations in place with three major pharmaceutical partners for these services and recently successfully completed a one year collaboration with another major pharmaceutical company. We plan to grow this business. We expect to supplement our GeneTrove services business with a subscription database, which we plan to launch later this year. The database will contain our proprietary gene function information, which is valuable in designing and prioritizing genomics-based drug discovery programs.

In addition to our antisense technology, our Ibis program and our GeneTrove genomics services business, we have a broad patent portfolio covering inventions in areas such as antisense chemistries, mechanisms by which antisense inhibitors work, gene sequences, antisense drugs in specific diseases, methods of performing our Ibis and GeneTrove businesses and manufacturing methods. We believe we have the largest antisense and RNA-oriented patent estate in the pharmaceutical industry with more than 700 patents issued or allowed. Beyond our RNA-based drug discovery patents, we have several other patents that have contributed substantial revenue to us. These patents include PNA antisense chemistry, reagents for diagnostics and novel immunogenicity applications of antisense. In 2000, we generated $12.3 million in revenue from the sale and license of patents unrelated to our core business.

ANTISENSE THERAPEUTICS

Our antisense drug research programs focus on targets associated with infectious, inflammatory and metabolic diseases and cancer. Once we have identified a gene target in one of these areas, we use its precise genetic sequence, or code, to design short synthetic strands of genetic code that precisely complement regions

of the code of the gene's RNA. Using high throughput methods, we are able to design and optimize these strands to rapidly identify the most effective inhibitor of the gene target. The product we've created, the synthetic strand of DNA, is called an antisense inhibitor to the target gene. We have pioneered and reduced to practice the design and optimization of antisense inhibitors targeting the RNA of genes.

Antisense inhibitors may be marketed as drugs because the inhibitor, once it binds to the target RNA, prevents the production of the disease-causing protein directly, resulting in a therapeutic benefit to the patient. We believe Antisense inhibitors are also useful as a tool to understand a gene's function and its value as a drug target. Understanding the function of a gene helps prioritize targets for drug discovery. Antisense is an efficient technology to convert gene sequence information into drugs. In addition, because antisense inhibitors are very specifically designed to complement the RNA of a gene, and as a result, do not inhibit unintended gene products, we believe antisense drugs are safer and more effective than traditional drugs. Our expertise in molecular biology and drug discovery allows us to rapidly identify potent antisense inhibitors of disease-causing proteins. Our medicinal chemistry program continues to focus on improving the properties of antisense drugs. Using chemical modifications we can design new antisense compounds that are potentially safer and more effective than current antisense drugs. In addition, we believe that these chemical modifications will support methods of dosing drugs that are more convenient for patients, including methods of oral delivery.

We brought the first antisense drug to market, Vitravene-TM-, for cytomegaloviral, or CMV, retinitis. We have a robust pipeline, including eleven products in development, seven of which are in human clinical trials and the remaining four of which we expect to enter clinical trials in the next twelve months. Our broad research programs continue to identify additional products that should keep our pipeline full.

GENETROVE GENOMICS

Our GeneTrove division uses antisense as a tool to provide valuable information about human genes: what they do, how they behave within cells, whether they are important in disease, and whether they would make good drug targets. The processes involved in answering these questions are called gene functionalization and target validation. In our GeneTrove division, we are using our antisense expertise to provide pharmaceutical companies with gene function and target validation information about genes that these companies are interested in targeting for drug discovery. Using our proprietary methods, we can provide this information rapidly and efficiently.

We currently have collaborations in place with three major pharmaceutical partners for our GeneTrove division. Our collaboration with Abbott began in 1998 and was recently extended, Aventis began in 1999, and R.W. Johnson Pharmaceutical Research Institute began in 2000. We recently completed our collaboration with AstraZeneca. With the vast amount of gene sequence information now available to pharmaceutical and biotechnology companies, there is significant demand for services such as ours in order to understand and prioritize the gene targets in drug discovery programs and expedite discovery of genomics-based drugs. We intend to grow our GeneTrove business this year by marketing the speed, accuracy and efficiency of our genomics capabilities to new partners. In addition to our functional genomics service business, our GeneTrove division expects to launch a subscription database later this year. This database will contain our proprietary gene function information and we expect that it will provide corporate partners with new methods to evaluate gene targets that are not currently available.

IBIS THERAPEUTICS

Ibis Therapeutics' drug discovery program targets the structured regions of RNA as the binding site for small molecule drugs. This novel program builds upon our substantial experience in RNA-targeted drug discovery and combines this understanding with innovations in comparative genomics, mass spectrometry and bioinformatics to discover low molecular weight, orally bioavailable drugs that work by binding to RNA.

We have developed proprietary algorithms and software to identify RNA structures that are important in disease to serve as targets for drugs. We can then use our proprietary molecular modeling techniques to predict the shape of drug binding pockets in these important RNA structures. With a working approximation of the shape of the target, our Ibis Therapeutics division is designing libraries of drug-like molecules that can

bind to the RNA targets. We use mass spectrometry to screen large numbers of small molecules against multiple RNA targets simultaneously. We are applying this drug discovery approach initially to discover novel antibacterial, antiviral and antifungal drugs, and we believe that our technology will be useful in a broad range of diseases such as cancer and central nervous system diseases. In 2000, Ibis initiated a research partnership with Pfizer worth up to $37 million. The funding is based on an up-front technology access fee, ongoing research support, and milestone payments for the first product. In addition, Pfizer will develop and commercialize drugs discovered through the collaboration and pay us milestone payments and royalties on the sale of these drugs.

In addition to the Pfizer partnership, Ibis has been funded through grants from the Defense Advanced Research Projects Agency, or DARPA, and the National Institute of Standards & Technology's Advanced Technology Program, or NIST. DARPA continues to invest in Ibis' approach as an opportunity to discover a universal antibacterial drug.

DRUG DISCOVERY AND DEVELOPMENT

Our work in RNA-based drug discovery and development has produced two important drug-discovery technologies: antisense and small molecule RNA drugs. 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 holds important potential to become a new alternative approach to traditional drug discovery.

ANTISENSE TECHNOLOGY PLATFORM

ANTISENSE DRUG DISCOVERY

Genes carry the information that cells need to produce proteins. Specific genes contain information to produce specific proteins at the genetic level. The human genome, and its collection of approximately 30,000 genes, contains the information required for the human body to produce all proteins. Genes are made up of DNA, a molecule that contains the information about when and how much of which protein to produce, depending on what function the gene is to perform. The DNA molecule is a double helix, a duplex of entwined strands. In each strand, the building blocks of DNA, the nucleotides, are bound or "paired" with complementary nucleotides on the other strand. The precise sequence of a nucleotide chain, called the "sense" sequence, is a blueprint for the information that is used during protein production. The sequence of a nucleotide chain that is precisely complementary to a given sense sequence is called its "antisense" sequence.

In the cell nucleus, the information in the gene necessary for the production of a protein is copied from one strand of DNA into precursor messenger RNA, or mRNA, through a process called transcription. After processing into mature mRNA, the mRNA moves from the nucleus of the cell into the cell cytoplasm, which contains amino acids, the building blocks of proteins. The information encoded in a single mRNA is then translated into many copies of the sequence of amino acids that builds the protein.

Using the information contained in mRNA, we design chemical structures, called oligonucleotides, which resemble DNA and are the complement of mRNA. These potent antisense oligonucleotides inhibit the production of disease-causing proteins. This method of drug design is highly productive. In eleven years we have created a substantial pipeline of drug candidates, including one product on the market and eleven products currently in development. We can design antisense drugs to be much more selective than traditional drugs. Antisense drugs are able to selectively inhibit one protein among a closely related group of proteins without having an impact on the other members of the group because antisense drugs interact by binding to mRNA and not, as traditional drugs do, by binding to proteins. As a result, we are able to design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique selectivity means that antisense drugs may be far less toxic than traditional drugs because they can be designed to minimize the impact on unintended targets.

Almost all human diseases are a result of inappropriate protein production or performance. By preventing the production of the disease-causing protein and acting in the early stage of the disease-causing

process, antisense drugs have the potential to provide greater therapeutic benefit than traditional drugs, which act after the body has produced the disease-causing protein. Traditional drugs are designed to interact with the proteins in the body that are supporting or causing a disease. Antisense technology is different than traditional drug discovery because it targets disease-causing proteins before the body produces them.

The design of antisense compounds is less complex, more rapid and more efficient than traditional drug design directed at protein targets. Traditional drug design usually begins by characterizing the three-dimensional structure of the protein target in order to design a prototype drug to interact with it. Proteins are complex molecules with structures that are difficult to predict. Antisense compounds, on the other hand, are designed to bind to mRNA structures, which are more easily understood and predicted. Prototype antisense drugs can be designed as soon as the sequence for the mRNA receptor is identified.

Our early research efforts focused on answering basic questions regarding antisense-based therapeutics, including their stability, their ability to be taken up by the target cells, their efficacy and their cost to manufacture. In the eleven years since our founding, we have made significant progress in understanding and using antisense technology to develop drug candidates, and have established a leadership position in this field.

GENETROVE TARGET VALIDATION AND GENE FUNCTIONALIZATION

Historically, the genomics industry has been focused on identifying and cataloging all of the genes in the human genome. This stage of the process is now complete. The next steps in the process of making drugs and creating value from genomics are to identify the functions of the approximately 30,000 human genes, or gene functionalization, and to identify which genes are good targets for drugs, or target validation. We have developed our GeneTrove division, which is responsible for providing our antisense target validation and gene functionalization information in an efficient and cost effective manner to the pharmaceutical industry.

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

Specialized technologies employed by our GeneTrove division include:

- A PROPRIETARY AUTOMATED RAPID THROUGHPUT SCREENING PROCESS THAT STREAMLINES THE CREATION OF OPTIMIZED, TARGET-SPECIFIC ANTISENSE INHIBITORS. We are using this system to build a large proprietary database of inhibitors to more than 1,800 gene targets this year and the capacity can continue to expand. We plan to use this system to identify antisense inhibitors to approximately 10,000 gene targets over the next several years. We are rapidly filing patent applications on the most important of these gene targets, thus expanding our proprietary position in gene function and antisense.

- LIBRARIES OF ANTISENSE INHIBITORS TO IDENTIFY NOVEL GENE FUNCTION. With hundreds, and planned thousands, of validated antisense inhibitors to individual genes in our library, we are able to screen the library to determine the function of individual genes in cell-based assays. Results from these screens can provide novel insights into functions of poorly understood genes, potentially identifying which genes are involved in disease. This process is being used to further expand our strong intellectual property estate.

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

- A PROPRIETARY BIOINFORMATICS DATABASE, WHICH WILL PROVIDE ACCESS TO CELLULAR PHENOTYPIC DATA TO PARTNERS. The data will be derived from evaluating antisense inhibitors for up to 10,000 genes in 20 or more cellular physiological tests. Partners may use this data to help to identify which genes are important drug targets. We expect to launch this subscription database later this year.

GeneTrove has already achieved many significant accomplishments. We have identified antisense inhibitors to more than 600 genes, patented many of these findings and expect to create antisense inhibitors to all important human genes over the next several years. As we create and test the inhibitors to these genes we are incorporating the data into our genomic database. We currently have three target validation and gene functionalization partnerships, with Abbott Laboratories, Aventis and Johnson & Johnson, and we are pursuing additional partnerships.

IBIS TECHNOLOGY PLATFORM

Ibis Therapeutics is our program to discover low molecular weight, potentially orally bioavailable drugs that work by binding to RNA. Ibis uses our success in pioneering RNA-targeted drug discovery and development and expands our ability to convert genomics data into drug discovery information. In Ibis, we have developed proprietary technologies in four key areas:

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

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

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

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

In our Ibis division, we are developing and integrating genome mining software to identify RNA structural motifs in therapeutic targets of interest. We can predict the three-dimensional shape of these motifs from biochemical probes of RNA structure and molecular modeling methods. We have made a fundamental breakthrough in the development of a parallel high-throughput screening strategy to identify small molecules that bind to RNA targets using high resolution mass spectrometry. In a MASS, multitarget affinity/specificity screening, assay, each compound and each target RNA is labeled by its exact molecular mass. Since every small molecule is labeled uniquely, a large mixture can be screened in the presence of several RNA targets simultaneously. The identity of the small molecule, the RNA target that it binds, its binding affinity and the location of the binding site on the RNA can be determined in one rapid set of experiments. Using this technology, we expect to be able to screen 10,000 compounds per day against ten RNA targets.

Our initial area of focus in Ibis is discovering novel antibacterial, antiviral and antifungal compounds. We believe the technology has the potential in diseases such as cancer and central nervous system disease. In 2000, Ibis and Pfizer entered into a research partnership worth up to $37 million.

PRODUCTS APPROVED AND UNDER DEVELOPMENT

Our antisense drug discovery programs identify compounds to treat cancer and infectious, inflammatory, and metabolic diseases. The following table outlines each product under development, its target, disease indication and development status, as well as our commercial rights.

PRODUCTS IN DEVELOPMENT

PRODUCT (1)	TARGET	DISEASE INDICATION	DEVELOPMENT STATUS	COMMERCIAL RIGHTS
Vitravene (I)	Antiviral	CMV Retinitis	Approved for marketing in the U.S., Europe, Australia and Brazil.	Isis/Novartis Ophthalmics (2)
ISIS 3521 (P)	PKC-(alpha)	Cancer - Non-Small Cell Lung Cancer, Others	Phase III	Isis
ISIS 2302 (P)	ICAM-1	Crohn's Disease	Phase II/III	Isis
ISIS 2302 (T)	ICAM-1	Psoriasis	Phase II	Isis
ISIS 14803 (P)	Antiviral	Hepatitis C	Phase I/II	HepaSense (3)
ISIS 2503 (P)	Ha-RAS	Cancer - Pancreatic, Others	Phase II	Isis
ISIS 5132 (P)	C-RAF kinase	Cancer - Ovarian, Others	Phase II	Isis
ISIS 104838 (P, O)	TNF-(alpha)	Rheumatoid Arthritis	Phase I	Isis/Orasense (4)
ISIS 104838 (T)	TNF-(alpha)	Psoriasis	Preclinical	Isis
ISIS 113715 (P, O)	PTP-1B	Diabetes	Preclinical	Isis
ISIS 13650 (I)	C-RAF kinase	Diabetic Retinopathy, Age-Related Macular Degeneration	Preclinical	Isis
ISIS 107248 (P, O)	VLA-4	Multiple Sclerosis, Inflammatory Diseases	Preclinical	Isis

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

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

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

(4) Orasense, a joint venture of Isis and Elan, owns the rights to an oral formulation of ISIS 104838.

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

CYTOMEGALOVIRUS, OR CMV, RETINITIS

Individuals with suppressed immune systems, such as those with AIDS resulting from the HIV virus, are susceptible to opportunistic infections caused by CMV. In the AIDS population, CMV retinitis is the primary cause of blindness. There are more than 270,000 active AIDS cases in the United States. The introduction of new anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, has prolonged survival in HIV-infected individuals. Over the last several years, this has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections including

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

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

HEPATITIS C, OR HCV

HCV continues to represent a major public health challenge. This potentially deadly disease affects the liver and can eventually cause liver cancer and death. It is estimated that almost four million people in the United States are infected with HCV and 8,000 to 10,000 people in the United States are expected to die from this disease each year. Interferon-(alpha) therapy, used alone or in combination with the drug ribovirin, is widely used in an attempt to eradicate this virus from chronically infected individuals, but long-term remissions are achieved in only about 20% of patients even after six months of therapy. 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. ISIS 14803 is designed to inhibit the replication of HCV. In preclinical studies, ISIS 14803 demonstrated specific reduction of the HCV RNA expression in both cell cultures and mouse model systems. We are developing ISIS 14803 under a joint venture agreement with Elan, which was signed in January 2000. The joint venture, HepaSense, will develop and commercialize this novel drug for HCV while investigating delivery of the drug with Elan's proprietary MEDIPAD Drug Delivery System, a disposable subcutaneous infusion device.

A Phase I/II clinical study of ISIS 14803 began in early 2000. This study in patients with Hepatitis C virus will evaluate both the safety and the efficacy of the drug. Patients in this Phase I/II trial receive ISIS 14803 intravenously. We plan to conduct studies of the subcutaneous delivery of ISIS 14803. We also plan to conduct studies of ISIS 14803 using Elan's MEDIPAD, a minimally invasive microinfusion pump. The MEDIPAD Drug Delivery System combines the convenience of a transdermal patch with the drug delivery capabilities of an infusion pump. This system can be self-administrated, is disposable and inexpensive. It can be used to infuse drug over 24 and 48-hour timeframes. Elan and its collaborators presently have multiple drugs in clinical trials being administered using the MEDIPAD System.

CANCER

We focus much of our work in the area of cancer on specific targets within multigene families believed to be involved in both normal and abnormal cell differentiation and cell growth. Members of multigene families, called isotypes, are extremely similar to one another at the protein level but most likely serve different biological functions. Since traditional drugs are not specific enough to inhibit one isotype within a family without affecting the function of the other related isotypes, it has been difficult to determine the functional differences among them. There is growing evidence that certain isotypes might be involved in abnormal cell differentiation or proliferation. Antisense drug discovery technology exploits the differences among the isotypes at the mRNA level to design drugs that can inhibit specific isotypes. Selective inhibition of a single isotype may result in less toxicity. Much of our work has focused on multigene families in the signal transduction pathway, the method by which various cellular and extra cellular proteins communicate information necessary for cell function and growth. Disruptions in the production or behavior of signal transduction proteins are involved in numerous proliferative disorders, including cancer.

Clinical trials of our anticancer compounds have demonstrated that antisense drugs appear to be promising cancer therapeutics. In these trials, our compounds were well tolerated, with none of the serious side effects associated with standard cancer chemotherapies, such as bone marrow or immune system suppression, gastrointestinal distress or hair loss.

ISIS 3521 ISIS 3521 is an antisense compound in Phase III clinical development which inhibits the production of one particular isotype, the (alpha) isotype, of protein kinase C. PKC is a key enzyme in signal transduction, and PKC isotypes are associated with both normal and abnormal cell growth. In the laboratory, we have been able to specifically inhibit the production of the PKC-(alpha) isotype without inhibiting the production of other isotypes, thus allowing the inhibition of an isotype believed to be involved in abnormal cell growth without more broadly affecting the PKC isotypes.

We are currently conducting a Phase III clinical trial of ISIS 3521 as an anticancer agent, using ISIS 3521 in combination with traditional cancer drugs. We initiated the Phase III trial in late 2000 for patients with non-small cell lung cancer, based on promising results in an on-going Phase II trial. Preliminary results from that trial showed a median survival of 19 months in patients with late stage non-small cell lung cancer. The typical median survival of these patients receiving standard chemotherapy alone for advanced non-small cell lung cancer is approximately eight months. In addition, patients treated in the Phase II study experienced minimal side effects attributable to ISIS 3521. In November 2000, the FDA granted ISIS 3521 fast track review status.

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

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

In Phase I studies, ISIS 2503 was well tolerated, with no significant side effects. We also observed evidence of activity. These results provided a basis for continuing development of ISIS 2503 in Phase II trials. In Phase II trials of ISIS 2503, we are evaluating the compound both alone and in combination with traditional cancer chemotherapies in patients with colon, breast, pancreatic and lung cancers. The colon cancer trial is near completion with no significant evidence of activity, while early results in lung cancer suggest improvement in cancer-related symptoms. We have completed a Phase I trial of ISIS 2503 plus a traditional chemotherapy drug and we are also planning a Phase II study in patients with cancer of the pancreas.

ISIS 5132 ISIS 5132 is an antisense compound which inhibits the expression of c-RAF kinase, another molecular target involved in cell signaling. C-RAF kinase is a member of the RAF kinase multi-gene family and is associated with abnormal cell growth. ISIS 5132 selectively inhibits c-RAF kinase without inhibiting the production of other members of that multigene family. Published results from a human clinical trial show that ISIS 5132 reduced the levels of its target RNA, c-RAF-1 after intravenous administration.

In Phase I clinical trials, ISIS 5132 showed evidence of antitumor activity in patients with ovarian, renal, pancreatic, and colon cancers. In those trials, ISIS 5132 was well-tolerated and caused no significant side effects. However, Phase II data in a variety of tumor types have shown minimal activity. We have limited future investment in this product, pending additional laboratory studies designed to identify the most promising areas for future development.

INFLAMMATORY DISEASES

Cell adhesion molecules make up a large family of related proteins and represent targets for treating inflammatory diseases. Inflammation is a key component of a large number of acute and chronic diseases. Although inflammation is part of a normal localized protective response that the human body uses to destroy infectious agents or repair injured tissue, disruptions of normal inflammatory responses often lead to inflammatory diseases. These inflammatory responses result in or contribute to a diverse set of diseases that can affect many organs of the body ranging from the skin to the brain. Common inflammatory diseases include rheumatoid arthritis, psoriasis, asthma and inflammatory bowel disease. Inflammation also occurs as a result of burn, shock or organ transplantation.

We have focused on a number of targets in our cell adhesion molecule program. Our most advanced cell adhesion research and development effort has been focused on the intercellular adhesion molecule, or ICAM, family and in particular, ICAM-1. ICAM-1 facilitates the migration of immune cells involved in both chronic and acute inflammation, allowing us to target both conditions. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, such as rheumatoid arthritis, asthma, psoriasis, organ transplant rejection and inflammatory bowel diseases. While it is unlikely that over-expression of ICAM-1 is the singular cause of these disorders, experts believe that ICAM-1 contributes to the pathology of these diseases and conditions. We have also identified lead compounds for other adhesion molecules including CD49d, or VLA-4.

In addition to cell adhesion molecules, we have active research programs targeting other steps in the inflammatory process. In particular, we have identified antisense inhibitors which selectively inhibit the expression of cytokines such as tumor necrosis factor-(alpha), or TNF-(alpha), interleukin 5, or IL-5, and the IL-5 receptor. Lead antisense compounds targeting mRNA for these proteins are showing promising activity in multiple models of inflammatory diseases.

ISIS 2302 ISIS 2302, the most advanced compound in our cell adhesion program, selectively inhibits ICAM-1 gene expression. In Phase I testing of ISIS 2302 in healthy volunteers, the compound was well tolerated at all doses. We conducted Phase II trials of ISIS 2302 in five diseases: Crohn's disease, psoriasis, ulcerative colitis, prevention of kidney transplant rejection and rheumatoid arthritis. The Phase II studies involved 20 to 40 patients each and, in general, were randomized and placebo-controlled.

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

  In late 1999, we completed a 300 patient pivotal-quality trial of ISIS 2302 in Crohn's disease, which we initiated based on positive results from a Phase II trial. In December 1999, we announced that the initial analysis of the data from this trial did not show efficacy and that, as a result, the data did not support an NDA filing. However, further analysis of the data indicated that those patients who received higher exposure to ISIS 2302 were more likely to experience complete clinical remission of their disease, which was the primary endpoint of the pivotal trial. We are planning additional clinical trials of ISIS 2302 in Crohn's disease patients using higher doses of ISIS 2302 to reproduce the drug exposure levels that correlated with higher response rates in the analysis. We expect to initiate patient enrollment in a Phase III trial in the second half of 2001.

- PSORIASIS In early 2000, we initiated a Phase II trial of ISIS 2302 in a topical cream formulation for psoriasis. We expect to present data from this trial in mid year 2001. Plaque psoriasis is the most common form of psoriasis, and is an uncomfortable, disfiguring and incurable skin disorder that affects two to four percent of the nation's population. Psoriasis produces recurrent skin lesions that may involve up to 80-90 percent of the body surface. A conveniently dosed topical cream formulation that is safe and effective would represent a significant improvement in treatment for patients and a significant commercial opportunity.

- OTHER INDICATIONS We have evaluated ISIS 2302 for several other indications, including rheumatoid arthritis, organ transplant rejection and ulcerative colitis. We completed a Phase II study in rheumatoid arthritis, in which we saw evidence of therapeutic activity. ISIS 2302 was well tolerated and the safety profile of the drug was attractive. However, we have decided to forego development of this product in favor of ISIS 104838, our second-generation antisense inhibitor of TNF-(alpha) for rheumatoid arthritis.

  We have completed a Phase II study for kidney transplant rejection. However, due to the competitive picture and the cost of development, we have put the development of ISIS 2302 for organ transplants on hold. We also plan to limit our investment in the development of ISIS 2302 as an enema formulation for treatment of ulcerative colitis.

ISIS 104838 ISIS 104838 is a second-generation antisense inhibitor of TNF-(alpha) and our first product from our proprietary second-generation chemistry to enter the clinic. In October 2000, we initiated Phase I clinical trials of ISIS 104838 to treat inflammatory and autoimmune diseases such as rheumatoid arthritis. We expect to begin Phase II trials of ISIS 104838 in patients with rheumatoid arthritis later this year. Our clinical program for ISIS 104838 investigates the safety and efficacy of the drug administered intravenously and subcutaneously. In addition, we expect to initiate clinical trials of topically administered ISIS 104838 in patients with psoriasis later this year. Orasense, a joint venture between Elan and us, is developing oral formulations of ISIS 104838 for rheumatoid arthritis and plans to test those solid dosage forms of ISIS 104838 in human clinical trials this year.

ISIS 113715 ISIS 113715 is a second-generation antisense inhibitor of the PTP-1B gene for Type 2 diabetes. The preclinical data demonstrate compelling activity in multiple diabetic animal models. The preclinical data package for ISIS 113715 suggests activity as an insulin sensitizer without causing hypoglycemia and while reducing cholesterol and weight gain. Potential corporate partners have replicated these results. We plan to initiate a Phase I trial in late 2001.

ISIS 13650 ISIS 13650 is an inhibitor of c-RAF kinase for diabetic retinopathy and age-related macular degeneration. ISIS 13650 is also a second-generation product in preclinical development. We plan to initiate Phase I clinical trials near the end of this year.

ISIS 107248 ISIS 107248 is a second-generation antisense inhibitor of CD49d or VLA-4. This compound, which we expect to evaluate as a possible treatment for a variety of inflammatory diseases including multiple sclerosis, is currently undergoing preclinical toxicology and pharmacokinetic studies.

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 development candidates. Our Ibis drug discovery program is currently focused on identifying broad-spectrum antibacterial agents with a focus on important drug-resistant infections.

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 the best lead compounds to advance into preclinical development. We are currently pursuing antisense and small molecule drug discovery programs focused on various anti-viral and anti-bacterial targets, inflammatory disease targets, and other key molecular targets that might play critical roles in cancer and metabolic diseases such as diabetes and obesity.

COLLABORATIVE ARRANGEMENTS AND LICENSING AGREEMENTS

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

ANTISENSE THERAPEUTICS

ELAN - HEPASENSE - HEPATITIS C

In January 2000, we formed with Elan a new subsidiary of Isis, HepaSense, to develop an antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus or HCV. We are the majority shareholder in HepaSense. HepaSense will develop and commercialize this novel therapeutic for HCV while investigating delivery of the drug with Elan's proprietary MEDIPAD Drug Delivery System, a disposable subcutaneous infusion device. The combination of a novel drug for HCV with a convenient delivery method could result in a very attractive product for this international public health problem. We are

currently conducting Phase II trials with ISIS 14803. Elan and we have each licensed significant technology to HepaSense. As part of the transaction, Elan purchased $7.5 million of our common stock at a premium to market. Elan may purchase an additional $7.5 million of common stock at a premium to our market price upon completion of a mutually agreed milestone. Elan also purchased our Series B preferred stock which is convertible in the future into either our stock or stock in HepaSense. As part of the transaction, we also issued warrants to Elan, which are exercisable in five years. In addition, Elan made available to us a $12.0 million line of credit for our funding commitment to HepaSense.

ELAN - ORASENSE - ORAL FORMULATION

In April 1999, we formed with Elan a new subsidiary, Orasense, to develop a platform technology for the oral delivery of antisense drugs. We are the majority shareholder in Orasense. The first oral drug Orasense is working on is ISIS 104838, our antisense inhibitor for TNF-(alpha). TNF-(alpha) is a gene that has been implicated in a wide range of inflammatory diseases. As part of the agreement, Elan made a $27 million equity investment in us, consisting of $15 million of common stock purchased at a premium to market and $12 million of convertible exchangeable preferred stock. Elan also received warrants exercisable in five years. Elan has the right to convert the preferred stock into either an ownership interest in us or in Orasense. As part of the agreement, Elan made available to us an $18.4 million line of credit for our funding commitment to Orasense.

We have made substantial progress in oral formulations of antisense drugs, achieving significant oral bioavailability by combining novel chemistries and formulation approaches. Elan, a world leader in oral drug delivery technology, has demonstrated the oral delivery and bioavailability of large macromolecules with properties similar to many antisense drugs. Both companies are combining existing technologies and expertise with new research efforts towards the goal of building a proprietary, platform technology for the oral delivery of antisense drugs.

ASTRAZENECA

In December 1998, we established an antisense collaboration with AstraZeneca to discover, develop and commercialize novel antisense drugs targeting specific genes associated with cancer. The initial term of this collaboration is three years, however AstraZeneca may terminate the agreement at the end of the second year. We received notice in December 2000 that AstraZeneca was terminating the agreement.

NOVARTIS OPHTHALMICS

In 1997, we entered into an agreement with Novartis Ophthalmics, formerly CIBA Vision Corporation, granting them exclusive worldwide distribution rights for Vitravene. The terms of the agreement allow for us to receive $20 million in pre-commercial fees and milestones. As of December 31, 2000, we have received $17.5 million of these pre-commercial fees and milestones. While Novartis Ophthalmics markets and sells Vitravene worldwide, we manufacture and sell Vitravene to Novartis Ophthalmics, at a price that allows us to share the commercial value of the product with them. The FDA approved Vitravene for commercial marketing in August 1998. In 1999 Vitravene received marketing approval in Europe and Brazil. Vitravene has also been approved for marketing in Australia. We delivered our first commercial shipment of Vitravene to Novartis Ophthalmics in August 1998.

OTHER

In June 1998, we established 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 will screen in its proprietary enzymatic assays for identifying Hepatitis C virus replication inhibitors. Merck has the right to commercialize any drugs arising from the collaboration, and we retain the right to use technology developed in the collaboration in our antisense program. The three-year collaboration provides us with annual research support plus a technology access fee, milestone payments and royalties upon commercialization. The collaboration ends in June 2001, however, we expect to enter into an extension of this agreement.

GENETROVE COLLABORATIONS

ASTRAZENECA

In January 2000, we entered into a target validation collaboration with AstraZeneca for a one year term. Through the collaboration, we used our target validation technology to assess and prioritize genes identified within AstraZeneca's genomics programs. This collaboration enabled AstraZeneca to determine the function and therapeutic value of novel gene targets and to potentially use this information about gene function to develop pharmaceutical products. It also provided us with valuable information on these targets to assist in our development of novel antisense drugs.

AVENTIS

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

ABBOTT LABORATORIES

In December 1998, we entered into a target validation collaboration with Abbott Laboratories, Inc. Through the collaboration, we are utilizing our target validation technology to enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Under the agreement, Abbott agreed to pay us an up-front fee, research fees, milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. We also received rights to develop drugs targeting Abbott proprietary genes for Abbott. The initial term of the collaboration was two years. Under the agreement, Abbott had the ability to extend the term of the agreement. In December 2000, both parties agreed to extend the term of the agreement for an additional two years.

R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

In July 2000, we entered into a target validation agreement with R.W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies. Under the collaboration, we are using our proprietary target validation technology to assess and prioritize genes identified within Johnson & Johnson's genomics programs. This collaboration enables Johnson & Johnson to determine the function and therapeutic value of novel gene targets and to potentially use this information about gene function to develop pharmaceutical products. It also provides us with valuable information on these targets to assist in our development of novel antisense drugs. The initial term of this collaboration is one year.

IBIS COLLABORATIONS

PFIZER

In June 2000, our Ibis division and Agouron Pharmaceuticals, Inc., a Pfizer company, entered into a collaboration for the discovery and development of small molecule drugs against certain RNA targets. Using Ibis' proprietary technology and Pfizer's expertise in small molecule drug discovery, the collaboration focuses on discovering drugs that bind to RNA. Pfizer will fund collaborative research, pay an up-front technology access fee and make milestone payments, totaling up to $37 million. In addition, Pfizer will develop and commercialize drugs discovered by the collaboration and will pay us royalties on sales of any drugs resulting from the collaboration.

LICENSING AGREEMENTS

COLEY PHARMACEUTICAL GROUP

In September 2000, we sold to Coley Pharmaceutical Group our patents concerning the use of phosphorothioate oligonucleotides for activating the immune system. The patents were originally licensed to Coley in 1998 for a limited scope of use, at which time Coley paid us $5 million. In exchange for all non-antisense rights to this group of immunomodulation patents and in lieu of any and all future payments that could potentially be owed under the original agreement, Coley paid us an additional $10.7 million.

PANTHECO

In September 2000, we entered into an agreement to license our novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Pantheco, on a nonexclusive basis to treat diabetes and cardiovascular diseases. Pantheco completed financing to raise funds to support its current business and to fund this expansion of therapeutic focus on October 18, 2000. Subsequent to the completion of Pantheco's financing, we received, as a fee for this license, 9 million DKK, or $1.1 million, which was paid in Pantheco shares. In addition, Pantheco will pay us royalties and milestones on any products developed using PNA. This is the second license of PNA technology from us to Pantheco. As part of the first licensing transaction completed in November 1998, we received an equity position in Pantheco.

ROCHE MOLECULAR SYSTEMS

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

MANUFACTURING

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

We have a 12,000 square foot Good Manufacturing Practices manufacturing facility located in Carlsbad, California. We believe we have sufficient manufacturing capacity to meet both current and future research and clinical needs both for ourselves and for our partners. We also believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated commercial needs. We also believe that with reasonably anticipated benefits from increases in scale, we will be able to manufacture antisense compounds at commercially competitive prices.

In 1998, we established an antisense oligonucleotide manufacturing collaboration with Avecia Life Science Molecules, a leading supplier of chemical and biological compounds to the pharmaceutical and biotechnology industries. Although the collaboration ended in January 2000, we continue to work with Avecia to establish an oligonucleotide supply relationship. Access to an alternate manufacturing source will provide us with greater flexibility in production scheduling and will reduce our risk of dependence on a single manufacturing site for all of our clinical needs. We are not required to make any capital investment to create this manufacturing capability.

In 1999, we established a commercial-scale manufacturing collaboration with Abbott Laboratories. This collaboration combines Abbott's process development expertise and manufacturing capability with our proprietary oligonucleotide manufacturing technology.

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 January 31, 2001, we had been issued or allowed more than 700 patents worldwide and had filed more than 635 patent applications in the United States, and counterparts of many of these applications in other countries. Patents issued to us or applied for cover the following types of inventions, processes and products:

- Composition of matter claims to core chemistries for oligonucleotide structures, which cover our rights to the building blocks of our compounds;
- Composition of matter claims to antisense compounds targeted to particular messenger 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, i.e., SAR by mass spectrometer; and
- Methods claims for rapidly discovering antisense oligonucleotides, which cover our rapid through-put method of discovering antisense oligonucleotides.

GOVERNMENT REGULATION

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

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

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

COMPETITION

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

Vitravene and our other products under development address numerous markets. Our competition has been and will continue to be determined in part by the diseases for which our compounds are developed and ultimately approved by regulatory authorities. For certain of our products, an important factor in competition may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market is an important competitive factor. We expect that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price and patent position.

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

EMPLOYEES

As of January 31, 2001, we employed 303 individuals, of whom 122 hold advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. None of our employees is covered by collective bargaining agreements, and management considers relations with its employees to be good.

EXECUTIVE OFFICERS

The following set forth certain information regarding our executive officers as of March 6, 2001:

NAME	AGE	POSITION
Stanley T. Crooke, M.D., Ph.D.	55	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall	45	Executive Vice President, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.	44	Vice President, Biology
Douglas L. Cole, Ph.D.	54	Vice President, Development Chemistry & Pharmaceutics
F. Andrew Dorr, M.D.	47	Vice President, Clinical Development & Chief Medical Officer
David J. Ecker, Ph.D.	46	Vice President & Managing Director, Ibis Therapeutics
Arthur A. Levin, Ph.D.	47	Vice President, Toxicology & Pharmacokinetics
Patricia Lowenstam	54	Vice President, Human Resources
Karen S. Lundstedt	36	Vice President, Investor Relations & Corporate Communications

STANLEY T. CROOKE, M.D., PH.D.
CHAIRMAN OF THE BOARD, PRESIDENT AND CHIEF EXECUTIVE OFFICER

Dr. Crooke was a founder of Isis and has been its Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke is Chairman of the Board of Idun Pharmaceuticals, Inc., a pharmaceutical company. He serves as a director of Valentis, Inc., SYNSORB Biotech Inc., and EPIX Medical, Inc. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

B. LYNNE PARSHALL
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 served as Vice President of Business Development of Biotrack, Inc., a medical device company, during 1988 and 1989. 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, BIOLOGY

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

DOUGLAS L. COLE, PH.D.
VICE PRESIDENT, DEVELOPMENT CHEMISTRY & PHARMACEUTICS

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

F. ANDREW DORR, M.D.
VICE PRESIDENT, CLINICAL DEVELOPMENT & CHIEF MEDICAL OFFICER

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

DAVID J. ECKER, PH.D.
VICE PRESIDENT & MANAGING DIRECTOR, IBIS THERAPEUTICS

Dr. Ecker was a founder of the Company and has served as our Vice President & Managing Director of Ibis Therapeutics, a division of Isis Pharmaceuticals, since June 1995. He served as our Vice President, Biology from July 1993 to June 1995, as our Executive Director, Molecular and Cellular Biology from February 1993 to July 1993, and as our Director, Molecular and Cellular Biology from February 1989 to February 1993. From

1984 until February 1989, he was employed by SmithKline and French Laboratories in a variety of research positions.

ARTHUR A. LEVIN, PH.D.
VICE PRESIDENT, TOXICOLOGY & PHARMACOKINETICS

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

PATRICIA LOWENSTAM
VICE PRESIDENT, HUMAN RESOURCES

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 S. LUNDSTEDT
VICE PRESIDENT, INVESTOR RELATIONS & 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.

RISK FACTORS

Please consider the following risk factors carefully in addition to the other information contained in this report.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN REGULATORY APPROVAL FOR OUR PRODUCTS.

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration regulations, and by comparable authorities in other countries, to show the safety and efficacy of each of our drug candidates, as well as the optimum dosage for each, before the FDA can approve a drug candidate for sale. We may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our products under development. Delays in receiving these approvals, failure by us or our partners to receive these approvals at all or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products.

OUR BUSINESS WILL SUFFER IF OUR PRODUCTS ARE NOT USED BY DOCTORS TO TREAT PATIENTS.

We cannot guarantee that any of our products in development, if approved for marketing, will be used by doctors to treat patients. We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. However, we may not be successful in commercializing additional products.

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

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the clinical efficacy and safety of our product candidates and their potential advantages over competitive products; and
- reimbursement policies of government and third-party payors.

In addition, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

OUR BUSINESS WILL SUFFER IF ANY OF OUR COLLABORATIVE PARTNERS FAIL TO DEVELOP, FUND OR SELL ANY OF OUR PRODUCTS UNDER DEVELOPMENT OR IF WE ARE UNABLE TO OBTAIN ADDITIONAL PARTNERS.

If any collaborative partner fails to develop or sell any product in which we have rights, our business may be negatively affected. While we believe that our collaborative partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in commercialized products. The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program.

Collaborative partners may be 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.

We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful.

OUR BUSINESS COULD SUFFER IF THE RESULTS OF CLINICAL TESTING INDICATE THAT ANY OF OUR PRODUCTS UNDER DEVELOPMENT ARE NOT SUITABLE FOR COMMERCIAL USE.

Drug discovery and development involves inherent risks, including the risk that molecular targets prove unsuccessful and the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings or have undesirable side effects. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development of drug candidates based upon antisense technology, a novel drug discovery tool for designing drugs that work at the genetic level to block the production of disease-causing proteins.

WE HAVE INCURRED LOSSES AND OUR BUSINESS WILL SUFFER IF WE FAIL TO ACHIEVE PROFITABILITY IN THE FUTURE.

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since we were founded in January 1989. As of December 31, 2000, our accumulated losses were approximately $311 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and we expect losses to increase as our preclinical testing and clinical trial efforts continue to expand. We cannot guarantee that we will successfully develop, receive regulatory approval for, commercialize, manufacture, market or sell any additional products, or achieve or sustain future profitability.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN TIMELY FUNDING.

Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the interest earned on those funds, will be adequate to satisfy our capital needs for at least the next three years. We expect that we will need substantial additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- 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;

- the costs involved in filing, prosecuting and enforcing patent claims;

- competing technological and market developments, including the introduction of new therapies that address our markets; and

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

Additional funds will need to be raised through public or private financing. Additional financing may not be available, or, if available, may not be available on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others if available. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

OUR BUSINESS WILL SUFFER IF WE CANNOT MANUFACTURE OUR PRODUCTS OR HAVE A THIRD PARTY MANUFACTURE OUR PRODUCTS AT LOW COSTS SO AS TO ENABLE US TO CHARGE COMPETITIVE PRICES TO BUYERS.

To establish additional commercial manufacturing capability on a large scale, we must improve our manufacturing processes and reduce our product costs. The manufacture of sufficient quantities of new drugs is typically a time-consuming and complex process. Pharmaceutical products based on chemically modified oligonucleotides have never been manufactured on a large commercial scale. There are 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. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

OUR BUSINESS WILL SUFFER IF WE FAIL TO COMPETE EFFECTIVELY WITH OUR COMPETITORS.

Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing other new therapeutic drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time to develop and commercialize our products, or to recover our research, development or commercialization expenses.

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 manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

OUR BUSINESS WILL SUFFER IF WE ARE UNABLE TO PROTECT OUR PATENTS OR OUR PROPRIETARY RIGHTS.

Our success depends to a significant degree upon our ability to develop proprietary products. However, patents may not be granted on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to offer meaningful protection. Furthermore, our issued patents or patents licensed to us could potentially be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

INTELLECTUAL PROPERTY LITIGATION COULD HARM OUR BUSINESS.

It is possible that we may have to defend our intellectual property rights in the future. In the event of an intellectual property dispute, we may be forced to litigate or otherwise defend our intellectual property assets. Disputes could involve litigation or proceedings declared by the United States 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 claimed an intellectual property right to technology we use, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all.

THE LOSS OF KEY PERSONNEL, OR THE INABILITY TO ATTRACT AND RETAIN HIGHLY SKILLED PERSONNEL, COULD ADVERSELY AFFECT OUR BUSINESS.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms, because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

OUR STOCK PRICE MAY CONTINUE TO BE HIGHLY VOLATILE.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. During the past twelve months, the market price of our common stock has ranged from $5.75 to $39.00 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

PROVISIONS IN OUR CERTIFICATE OF INCORPORATION, OTHER AGREEMENTS AND DELAWARE LAW MAY PREVENT STOCKHOLDERS FROM RECEIVING A PREMIUM FOR THEIR SHARES.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66-2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the president, or by any holder of 10% or more of our outstanding common stock. These provisions, as well as Delaware law and other of our agreements including our stockholders' Rights Plan, 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 Isis without action by the stockholders.

ITEM 2. PROPERTIES

We occupy approximately 170,000 square feet of laboratory and office space, including a 12,000 square foot Good Manufacturing Practices manufacturing suite, in five buildings located on our "campus" in Carlsbad, California. We own three of these buildings and, as of December 31, 2000, these buildings secured approximately $7 million of our debt. We lease two of the buildings under lease agreements expiring in 2007 and 2010. We have also leased 1,600 sq. ft. of office space in the United Kingdom to accommodate employees supervising European clinical trials. However, we are in the process of closing our United Kingdom office. We believe that our facilities will be adequate to meet our needs through 2001.

ITEM 3. LEGAL PROCEEDINGS

The company is not party to any material legal proceedings.

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 "ISIP." 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
1999		
First Quarter	$ 15.25	$ 8.94
Second Quarter	$ 12.19	$ 9.25
Third Quarter	$ 13.81	$ 9.16
Fourth Quarter	$ 17.38	$ 3.88
2000		
First Quarter	$ 39.00	$ 5.75
Second Quarter	$ 16.25	$ 8.06
Third Quarter	$ 15.75	$10.50
Fourth Quarter	$ 14.75	$ 8.81

As of January 12, 2001, there were approximately 1,129 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future. Under the terms of certain term loans, we are restricted from paying cash dividends until the loans are fully repaid. See Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations - Liquidity and Capital Resources."

RECENT SALES OF UNREGISTERED SECURITIES

On January 14, 2000, in conjunction with the formation of our HepaSense joint venture, we sold 12,015 shares of our Series B Convertible Preferred Stock to Elan International Services for $12,015,000. In conjunction with this transaction, we also sold 297,619 shares of our Common Stock to EIS for $7,500,000, and issued to EIS a warrant to purchase up to 14,881 shares of our Common Stock at $50.40 per share. The term of the warrant is

5 years. We expect to use the proceeds from the sale of these securities for general corporate purposes, including, but not limited to, funding the research and development activities of the HepaSense joint venture.

At any time after June 30, 2002, the Preferred Stock (including accrued dividends) will be convertible at EIS' option into shares of our Common Stock at 125% of the 60-trading day average closing price of our Common Stock ending two business days prior to June 30, 2002 (as adjusted for stock splits, stock dividends and the like). In the event of a liquidation of Isis or certain transactions involving a change of control of Isis, the agreement provides for automatic conversion of the Preferred Stock on terms similar to those set forth above.

At any time after January 14, 2000, the holders of Preferred Stock may exchange their Preferred Stock with us for preferred shares of HepaSense held by us that represent 30.1% of the total outstanding capital stock of HepaSense. The exchange right will terminate if the Preferred Stock is converted into our Common Stock, unless such conversion occurs as a result of a liquidation or certain transactions involving a change of control of Isis.

Until July 14, 2002, EIS will, at our request, purchase our convertible debt in an amount equal to our share of budgeted funding for HepaSense. The convertible debt will have a term of six years, bear interest at the rate of 12% and be convertible into our Common Stock at a premium. We may prepay the convertible debt in cash or in our Common Stock. We will use the proceeds of the sale of the convertible debt to provide additional development funding to HepaSense.

The issuance and sale of these securities was intended to be exempt from registration and prospectus delivery requirements under the Securities Act of 1933, as amended, by virtue of Section 4(2) thereof due to, among other things, (i) the limited number of persons to whom the shares were issued, (ii) the distribution of disclosure documents to the investor, (iii) the fact that such person represented and warranted to Isis, among other things, that such person was acquiring the shares for investment only and not with a view to the resale or distribution thereof, and (iv) the fact that certificates representing the shares were issued with a legend to the effect that such shares had not been registered under the Securities Act or any state securities laws and could not be sold or transferred in the absence of such registration or an exemption therefrom.

ITEM 6. SELECTED FINANCIAL DATA (IN THOUSANDS, EXCEPT PER SHARE AMOUNTS)

	YEARS ENDED DECEMBER 31,				
	2000	1999	1998	1997	1996
STATEMENT OF OPERATIONS DATA:					
Research and development revenues (includes license and royalty revenue)	$ 37,255	$ 33,925	$ 39,171	$ 32,722	$ 22,663
Research and development expenses	$ 57,014	$ 66,413	$ 62,200	$ 55,940	$ 45,653
Net loss applicable to common stock	$ (54,699)	$ (59,645)	$ (42,983)	$ (31,066)	$ (26,521)
Basic and diluted net loss per share	$ (1.48)	$ (2.08)	$ (1.60)	$ (1.17)	$ (1.04)
Shares used in computing basic and diluted net loss per share	37,023	28,703	26,873	26,456	25,585

	DECEMBER 31,				
	2000	1999	1998	1997	1996
BALANCE SHEET DATA:					
Cash, cash equivalents and short-term investments	$ 127,262	$ 52,839	$ 58,848	$ 86,786	$ 77,624
Working capital	$ 118,568	$ 44,213	$ 40,651	$ 62,573	$ 56,300
Total assets	$ 183,256	$ 103,107	$ 96,074	$ 117,881	$ 101,305
Long-term debt and capital lease obligations, less current portion	$ 102,254	$ 87,254	$ 77,724	$ 56,452	$ 19,864
Accumulated deficit	$ (311,460)	$ (256,761)	$ (197,116)	$ (154,133)	$ (123,067)
Stockholders' equity (deficit)	$ 66,366	$ 869	$ (4,186)	$ 34,852	$ 58,385

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Since our inception in January 1989, almost all of our resources have been devoted to our research, drug discovery and drug development programs. We are not yet profitable and expect to continue to have operating losses for at least the next several years. Our revenue comes from collaborative research and development agreements with pharmaceutical companies, the sale and licensing of our intellectual property, research grants and interest income. The revenue from the collaboration agreements increases the amount of research and development activity that we are able to fund and offsets a portion of our research and development costs. See Item 1, Business - Collaborative Arrangements and Licensing Agreements. In 1998, we received approval from the U.S. Food and Drug Administration, or FDA, to begin marketing our first product, Vitravene, a drug used to treat CMV retinitis.

RESULTS OF OPERATIONS

YEARS ENDED DECEMBER 31, 2000 AND DECEMBER 31, 1999

Total revenue for the year ended December 31, 2000 was $37.3 million, compared to $33.9 million for 1999. The 10% increase in revenues for the year was due primarily to our sale of patents to Coley Pharmaceutical Group; the licensing of our third generation antisense chemistry to Pantheco A/S; our collaborations with Agouron Pharmaceuticals, Inc., a Pfizer Company and Aventis; our two joint ventures with Elan Corporation, plc, Orasense and HepaSense, and certain government grants and contracts. The increase was partially offset by the conclusion in December 1999 of development funding from Novartis Pharma AG and Boehringer Ingelheim International GmbH.

Our revenue from collaborative research and development agreements was $16.9 million for the year ended December 31, 2000, compared with $29.4 million in 1999, a decrease of 43%. The decrease was principally due to the conclusion in December 1999 of development funding from Novartis and Boehringer Ingelheim. We delivered our first commercial shipment of Vitravene to our partner Novartis Ophthalmics in 1998. Since August 1998 we have earned $674,000 in revenue related to shipments of Vitravene to Novartis Ophthalmics.

In January 2000, we formed a joint venture with Elan to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus. The joint venture, HepaSense, is a Bermuda limited company. This is our second joint venture with Elan. We formed our first joint venture with Elan, Orasense, in April 1999. While we own 80.1% of the outstanding common stock of each of the joint ventures, HepaSense and Orasense, Elan and its subsidiaries have retained in each of the joint ventures significant minority investor rights that are considered "participating rights" as defined in EITF 96-16. Therefore, we do not consolidate the financial statements of HepaSense or Orasense, but instead account for our investment in HepaSense and Orasense under the equity method of accounting. During 2000, we recognized $8.0 million in contract revenue for research and development activities performed for HepaSense and Orasense. In 1999, we recognized $4.4 million in contract revenue for research and development activities we performed for Orasense.

Our revenue from licensing and royalty activities was $12.4 million in 2000 of which $10.7 million was from the sale of certain of our patents to Coley Pharmaceutical Group. Licensing and royalty revenue in 1999 was insignificant.

Research and development expenses decreased by 14% to $57.0 million in 2000, from $66.4 million in 1999. The significant decrease in expenses was primarily due to our restructuring and staff reductions that occurred earlier in 2000 offset by expenses related to the initiation of Phase III clinical trials for ISIS 3521 in non-small cell lung cancer. We expect that research and development expenses will increase from the 2000 levels as we advance our pipeline into later and more expensive stages of development. Of the eleven products we currently have in development, six of them are in either Phase II or Phase III clinical trials.

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

general and administrative expenses will increase from the 2000 levels in support of our increasing research and development activities.

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

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

Interest expense increased to $13.2 million in 2000, compared with $11.4 million in 1999. This increase in interest expense was due primarily to borrowings under the $18.4 million and $12.0 million convertible debt facilities available to us from Elan to fund research and development activities for Orasense and HepaSense, respectively. During 2000, we borrowed $6.7 million from Elan related to Orasense and $1.8 million from Elan related to HepaSense. The terms of the Elan debt provide that the payment of principal and interest is deferred until maturity in 2005 and 2006 for Orasense and HepaSense, respectively. In 2000, $9.7 million of the $13.2 million in interest expense, which was accrued under various long-term debt agreements, will not require current cash payment.

Our net operating loss of $30.6 million in 2000 was 29% lower than our net operating loss of $43.1 million in 1999 for the reasons stated earlier. During 2001 we expect to be conducting two pivotal Phase III clinical trial programs: the ongoing trial of ISIS 3521 in patients with non-small cell lung cancer and the planned trial of ISIS 2302 in patients with Crohn's disease. These programs, in addition to the continued aggressive development of our large pipeline, will result in increased expenses and lead to an increase in our net loss from operations in 2001. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition. Our 2000 loss applicable to common stock was $54.7 million, compared to $59.6 million in 1999. The 2000 loss applicable to common stock included $15.9 million for our equity in the losses of Orasense and HepaSense and $0.3 million for our equity in the loss of Pantheco. The 1999 loss applicable to common stock included $7.2 million for our equity in the loss of Orasense.

At December 31, 2000, our net operating loss carryforward for federal income tax purposes was approximately $295.5 million. The net operating loss and research credit carryforwards make up the majority of our deferred tax assets. We will only be able to use the net operating loss and research credits, and realize the benefit of these deferred tax assets, if we become profitable. We have fully reserved all of our deferred tax assets, as their realization is uncertain. Our research credit carryforward for federal income tax purposes was approximately $13.2 million. 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.

We believe that inflation and changing prices have not had a material effect on our operations to date.

YEARS ENDED DECEMBER 31, 1999 AND DECEMBER 31, 1998

Our total revenue was $33.9 million for the year ended December 31, 1999, compared with $39.2 million in 1998. The decrease was principally due to $5.0 million of revenue recognized in 1998 from licensing certain patents. Revenue earned in 1999 from licensing patents was not significant. During 1999, we recognized $4.4 million in contract revenue for research and development activities performed for Orasense. We delivered our first commercial shipment of Vitravene to our partner Novartis Ophthalmics in 1998, earning

product revenue of $0.6 million. No commercial shipments of Vitravene were made in 1999, and no product revenue was earned.

Research and development expenses were $66.4 million in 1999, compared to $62.2 million in 1998. The increase in research and development expenses occurred because compounds in preclinical and clinical development continued to advance into later and more expensive stages of development during 1999. Operating expenses in 1998 included a $5.2 million write-off of acquired patents. No similar expenses were incurred in 1999.

General and administrative expenses were $10.6 million for 1999, compared with $9.5 million in 1998. This increase was primarily due to expanded business development and investor relations activities in support of our increasing research and development efforts.

Interest income declined to $2.5 million in 1999 from $4.2 million in 1998. This decrease was primarily due to lower levels of cash and short-term investments during 1999.

Interest expense increased to $11.4 million in 1999, compared with $9.4 million in 1998. This increase in interest expense was due primarily to borrowing a total of $40 million in 1997 and 1998 under the terms of ten-year private debt financings. Under the terms of the private debt financing arrangements, payment of both principal and interest is deferred for the first five years. During the third and fourth quarters of 1999, the company also borrowed $2.3 million from Elan related to the Orasense joint venture. The terms of the Elan debt also provide that the payment of principal and interest is deferred until maturity in 2005. Therefore, of the $11.4 million interest expense in 1999, $8.1 million was accrued under long-term debt agreements and will not require current cash payment.

Our net loss applicable to common stock for 1999 was $59.6 million, or $2.08 per share, compared to $43.0 million, or $1.60 per share, for 1998. The 1999 loss included $7.2 million for equity in the loss of Orasense. Our loss from operations was $43.1 million in 1999, compared to $37.8 million in 1998.

LIQUIDITY AND CAPITAL RESOURCES

We have financed our operations with revenue from contract research and development, revenue from the sale or licensing of our intellectual property, the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2000, we have earned approximately $217 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 $368 million from the sale of equity securities. We have borrowed approximately $82.3 million under long-term debt arrangements to finance a portion of our operations.

As of December 31, 2000, we had cash, cash equivalents and short-term investments of $127.3 million and working capital of $118.6 million. In comparison, we had cash, cash equivalents and short-term investments of $52.8 million and working capital of $44.2 million as of December 31, 1999. This increase in cash and short term investments resulted primarily from the sale of common and preferred stock to institutional investors, the exercise of stock options by our employees and borrowings under our long term debt arrangements. During 2000, we used $23.2 million in cash for operating requirements. Other significant cash uses included $20.6 million related to our investment in our affiliates, $3.9 million in principal payments on debt and capital lease obligations, $3.2 million for patent costs and $1.6 million for purchases of property and equipment.

Under the terms of our agreements with Elan, Elan will provide us with up to $18.4 million and $12.0 million in convertible debt to support our research and development activities related to Orasense and HepaSense, respectively. Restrictions on the availability of the debt facility are based on the anticipated collaboration costs and the balance of the funds available under each facility. As of December 31, 2000, the outstanding balance under the Elan line of credit facilities was $9.7 million and $1.9 million for Orasense and HepaSense, respectively. See Note 3 to the Financial Statements, "Long-term Obligations and Commitments."

In 1997 and 1998, we borrowed a total of $40 million in private transactions. The loans must be repaid on November 1, 2007, and bear interest at 14% per annum. No payments of either principal or interest are

required during the first 5 years of the loans. After the first 5 years, interest must be paid quarterly until the end of the loans. No principal payments are required until November 1, 2007. In conjunction with this transaction, we issued warrants to purchase 800,000 shares of common stock at a price of $25 per share. The warrants issued in connection with these financings expire on November 1, 2004. The warrants have been valued at a combined total of $5.4 million. This amount has been credited to stockholders' equity. Because interest is deferred during the first 5 years, the combined principal balance of both borrowings will accrue to a total of $78 million on November 1, 2002. The debt under these arrangements is carried on the balance sheet net of the unamortized amount allocated to the warrants and including accrued interest. The combined carrying amount of these notes at December 31, 2000 was $58.0 million. See Note 3 to the Financial Statements, "Long-term Obligations and Commitments".

As of December 31, 2000, our long-term obligations, including the current portions, totaled $106.9 million, compared to $91.1 million at December 31, 1999. This increase was due to the accrual of interest on the private debt financing together with the additional debt acquired during the year as described above. Additional capital lease financing to fund equipment acquisitions also contributed to the increase. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our business. We will continue to use lease lines as long as the terms continue to remain commercially attractive. We believe that our existing cash, cash equivalents and short-term investments, combined with interest income and committed contract revenue will be sufficient to meet our anticipated requirements for at least three years.

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, our 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. A hypothetical 100 basis point adverse move in interest rates along the entire interest rate yield curve would not materially affect the fair value of our interest sensitive financial instruments. Declines in interest rates over time will, however, reduce our interest income while increases in interest rates over time will increase our interest expense.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

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

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS

The information required by this item (with respect to Directors) is incorporated by reference from the information under the caption "Election of Directors" contained in our definitive Proxy Statement (the "Proxy Statement") which will be filed on or about February 28, 2001 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2000 Annual Meeting of stockholders to be held on April 6, 2001.

The required information concerning our Executive Officers is contained in Item 1, Part I of this Report.

ITEM 11. EXECUTIVE COMPENSATION

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

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

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

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

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

PART IV

ITEM 14. EXHIBITS, FINANCIAL STATEMENT SCHEDULES, AND REPORTS ON FORM 8-K

(a)(1) INDEX TO FINANCIAL STATEMENTS

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

(a)(2) INDEX TO FINANCIAL STATEMENT SCHEDULES

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

(a)(3) INDEX TO EXHIBITS

See Index to Exhibits on pages 32 through 33.

(b) REPORTS ON FORM 8-K

On December 12, 2000, the registrant filed a report on Form 8-K relating to the adoption of a stockholder rights plan.

(c) EXHIBITS

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

(d) FINANCIAL STATEMENT SCHEDULES

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

SIGNATURES

Pursuant to the requirements of Section 14 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 26th day of February, 2001.

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, Chief Executive Officer and Director (Principal executive officer)	February 26, 2001
/s/ B. LYNNE PARSHALL B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Director (Principal financial and accounting officer)	February 26, 2001
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	February 26, 2001
/s/ WILLIAM R. MILLER William R. Miller	Director	February 26, 2001

SIGNATURES	TITLE	DATE
/s/ MARK B. SKALETSKY Mark B. Skaletsky	Director	February 26, 2001
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 26, 2001

INDEX TO EXHIBITS

EXHIBIT NUMBER			DESCRIPTION OF DOCUMENT
1.1		-	Form of Common Stock Purchase Agreement between the Registrant and Ridgeway Investment Limited. (16)
3.1		-	Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
3.2		-	Bylaws. (1)
3.3		-	Certificate of Designation of the Series A Convertible Preferred Stock. (11)
3.4		-	Certificate of Designation of the Series B Convertible Preferred Stock. (14)
3.5		-	Certificate of Designation of the Series C Junior Participating Preferred Stock. (17)
4.1		-	Reference is made to Exhibits 3.1 through 3.5.
4.2		-	Specimen Stock Certificate. (1)
4.3		-	Specimen Series A Preferred Stock Certificate. (18)
4.4		-	Specimen Series B Preferred Stock Certificate. (18)
4.5		-	Form of Right Certificate. (17)
10.1		-	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule. (1)
10.2	*	-	Registrant's 1989 Stock Option Plan, as amended. (6)
10.3	*	-	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended. (4)
10.4	*	-	Form of Performance-Based Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan entered into between the Registrant and certain of its officers together with related schedule.
10.5	*	-	Registrant's Employee Stock Purchase Plan. (10)
10.6	*	-	Form of Employee Assignment of Patent Rights. (1)
10.7	*	-	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan. (10)
10.8	*	-	Severance Agreement dated January 11, 2000 entered into between the Registrant and its executive officers, together with related schedule. (10)
10.9		-	Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (2)
10.10		-	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (3)
10.11		-	Agreement between the Registrant and CIBA Vision Corporation (now Novartis Ophthalmics) dated July 10, 1997 (with certain confidential information deleted). (5)
10.12		-	Amendment No. 2 to the Agreement between the Registrant and CIBA Vision Corporation, dated September 14, 1998 (with certain confidential information deleted). (8)
10.13		-	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)
10.14		-	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)
10.15		-	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)
10.16		-	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)
10.17		-	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted). (6)
10.18		-	Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted). (7)
10.19		-	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted). (9)
10.20		-	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,

EXHIBIT NUMBER		DESCRIPTION OF DOCUMENT
		Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreements and License Agreements. (12)
10.21	-	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant; together with related Amendment to the Stock Purchase Agreement. (13)
10.22	-	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)
10.23	-	Agreement between the Registrant and Agouron Pharmaceuticals, dated June 9, 2000 (with certain confidential information deleted). (15)
10.24	-	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company. (17)
23.1	-	Consent of Ernst & Young LLP, Independent Auditors.
24.1	-	Power of Attorney. Reference is made to page 30.
99.1	-	Form of Confidentiality Agreement. (11)

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
(2) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.
(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1995 and incorporated herein by reference.
(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.
(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.
(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.
(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.
(8) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1998 and incorporated herein by reference.
(9) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.
(10) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.
(11) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.
(12) Filed as an exhibit to the Registrant's Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.
(13) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.
(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000 and incorporated herein by reference.
(15) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2000 and incorporated herein by reference.
(16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-90811) or amendment thereto and incorporated by reference.
(17) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.
(18) Filed as an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.

* 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, 2000 and 1999, and the related statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2000. 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, 2000 and 1999, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2000, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

San Diego, California
February 2, 2001

ISIS PHARMACEUTICALS, INC.
BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

	DECEMBER 31, 2000	DECEMBER 31, 1999
Current assets:		
Cash and cash equivalents	$ 39,615	$ 35,296
Short-term investments	87,647	17,543
Contracts receivable	3,346	5,429
Prepaids and other current assets	2,596	929
Total current assets	133,204	59,197
Property, plant and equipment, net	22,625	23,945
Patent costs, net	13,815	11,250
Investments in affiliates	12,491	6,991
Deposits and other assets	1,121	1,724
Total assets	$ 183,256	$ 103,107

LIABILITIES AND STOCKHOLDERS' EQUITY

Current liabilities:		
Accounts payable	$ 2,231	$ 3,148
Accrued compensation	3,598	1,215
Accrued liabilities	1,429	2,563
Deferred contract revenues	2,771	4,166
Current portion of long-term obligations	4,607	3,892
Total current liabilities	14,636	14,984
Long-term obligations, less current portion	102,254	87,254
Commitments		
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares authorized, issued and outstanding at December 31, 2000 and 1999	12,015	12,015
Accretion of Series A Preferred stock dividends	1,050	420
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at December 31, 2000 and no shares issued and outstanding at December 31, 1999	12,015	-
Accretion of Series B Preferred stock dividends	584	-
Common stock, $.001 par value; 50,000,000 shares authorized, 40,086,000 shares and 31,613,000 shares issued and outstanding at December 31, 2000 and 1999, respectively	40	32
Additional paid-in capital	352,854	245,192
Deferred compensation	(858)	-
Accumulated other comprehensive income (loss)	126	(29)
Accumulated deficit	(311,460)	(256,761)
Total stockholders' equity	66,366	869
	$ 183,256	$ 103,107

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
STATEMENTS OF OPERATIONS
(IN THOUSANDS, EXCEPT FOR PER SHARE AMOUNTS)

	YEARS ENDED DECEMBER 31,		
	2000	1999	1998
Revenues:			
Research and development revenues under collaborative agreements	$ 16,912	$ 29,357	$ 34,130
Research and development revenues from affiliates	7,967	4,402	-
Licensing and royalty revenues	12,376	166	5,041
Total revenue	37,255	33,925	39,171
Expenses:			
Research and development (not including compensation related to stock options of $435 for the year ended December 31, 2000)	57,014	66,413	62,200
General and administrative (not including compensation related to stock options of $152 for the year ended December 31, 2000)	8,644	10,571	9,511
Write-off of acquired patents	-	-	5,238
Compensation related to stock options	587	-	-
Restructuring activities	1,635	-	-
Total operating expenses	67,880	76,984	76,949
Loss from operations	(30,625)	(43,059)	(37,778)
Equity in loss of affiliates	(16,224)	(7,242)	-
Interest income	6,524	2,500	4,150
Interest expense	(13,160)	(11,424)	(9,355)
Net loss	(53,485)	(59,225)	(42,983)
Accretion of dividends on preferred stock	(1,214)	(420)	-
Net loss applicable to common stock	$ (54,699)	$ (59,645)	$ (42,983)
Basic and diluted net loss per share	$ (1.48)	$ (2.08)	$ (1.60)
Shares used in computing basic and diluted net loss per share	37,023	28,703	26,873

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
YEARS ENDED DECEMBER 31, 2000, 1999 AND 1998
(IN THOUSANDS)

DESCRIPTION	PREFERRED STOCK SHARES	PREFERRED STOCK AMOUNT	PREFERRED STOCK DIVIDEND ACCRETION	COMMON STOCK SHARES	COMMON STOCK AMOUNT	ADDITIONAL PAID IN CAPITAL	DEFERRED COMPENSATION
Balance at December 31, 1997	--	$ --	$ --	26,655	$ 27	$ 188,793	$ --
Comprehensive Loss							
Net loss	--	--	--	--	--	--	--
Change in unrealized gains and (losses)	--	--	--	--	--	--	--
Comprehensive loss	--	--	--	--	--	--	--
Options exercised and employee stock purchase plan	--	--	--	398	--	2,298	--
Issuances of warrants to purchase common stock	--	--	--	--	--	1,646	--
Balance at December 31, 1998	--	--	--	27,053	27	192,737	--
Comprehensive Loss							
Net loss	--	--	--	--	--	--	--
Change in unrealized gains and (losses)	--	--	--	--	--	--	--
Comprehensive loss	--	--	--	--	--	--	--
Issuance of preferred stock, Series A	120	12,015	--	--	--	--	--
Dividends accrued on preferred stock	--	--	420	--	--	--	--
Issuances of common stock, net of repurchases and offering costs	--	--	--	3,974	4	49,051	--
Warrants exercised	--	--	--	157	--	17	--
Options exercised and employee stock purchase plan	--	--	--	429	1	3,250	--
Compensation relating to the granting of options	--	--	--	--	--	137	--
Balance at December 31, 1999	120	12,015	420	31,613	32	245,192	--
Comprehensive Loss							
Net loss	--	--	--	--	--	--	--
Change in unrealized gains and (losses)	--	--	--	--	--	--	--
Comprehensive loss	--	--	--	--	--	--	--
Issuance of preferred stock, Series B	12	12,015	--	--	--	--	--
Dividends accrued on preferred stock	--	--	1,214	--	--	--	--
Deferred compensation	--	--	--	--	--	1,445	(1,445)
Issuances of common stock, net of offering costs	--	--	--	6,600	6	91,483	--
Options exercised and employee stock purchase plan	--	--	--	1,873	2	14,734	--
Compensation relating to the granting of options	--	--	--	--	--	--	587
Balance at December 31, 2000	132	$24,030	$ 1,634	40,086	$ 40	$352,854	$ (858)

DESCRIPTION	ACCUMULATED OTHER COMPREHENSIVE INCOME/(LOSS)	ACCUMULATED DEFICIT	TOTAL STOCKHOLDERS EQUITY (DEFICIT)
Balance at December 31, 1997	$ 165	$(154,133)	$ 34,852
Comprehensive Loss			
Net loss	--	(42,983)	(42,983)
Change in unrealized gains and (losses)	1	--	1

Comprehensive loss	--	--	(42,982)
Options exercised and employee stock purchase plan	--	--	2,298
Issuances of warrants to purchase common stock	--	--	1,646
Balance at December 31, 1998	166	(197,116)	(4,186)
Comprehensive Loss			
Net loss	--	(59,645)	(59,645)
Change in unrealized gains and (losses)	(195)	--	(195)
Comprehensive loss	--	--	(59,840)
Issuance of preferred stock, Series A	--	--	12,015
Dividends accrued on preferred stock	--	--	420
Issuances of common stock, net of repurchases and offering costs	--	--	49,055
Warrants exercised	--	--	17
Options exercised and employee stock purchase plan	--	--	3,251
Compensation relating to the granting of options	--	--	137
Balance at December 31, 1999	(29)	(256,761)	869
Comprehensive Loss			
Net loss	--	(54,699)	(54,699)
Change in unrealized gains and (losses)	155	--	155
Comprehensive loss	--	--	(54,544)
Issuance of preferred stock, Series B	--	--	12,015
Dividends accrued on preferred stock	--	--	1,214
Deferred compensation	--	--	
Issuances of common stock, net of offering costs	--	--	91,489
Options exercised and employee stock purchase plan	--	--	14,736
Compensation relating to the granting of options	--	--	587
Balance at December 31, 2000	$ 126	$(311,460)	$ 66,366

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	YEARS ENDED DECEMBER 31,		
	2000	1999	1998
Operating activities:			
Net loss	$ (53,485)	$ (59,225)	$ (42,983)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	5,535	5,196	4,258
Compensation related to stock options	587	137	--
Deferred interest on long term debt	9,685	8,077	6,112
Equity in losses of affiliates	16,224	7,242	--
Equity in affiliate received in exchange for patent licensing	(1,125)	--	--
Write-off of acquired patents	--	--	5,238
Write-off of inventory	301	--	--
Changes in operating assets and liabilities:			
Contracts receivable	2,083	(1,963)	(3,177)
Prepaids and other assets	(1,604)	220	1,172
Accounts payable	(917)	171	134
Accrued compensation	2,383	(1,873)	846
Accrued liabilities	(1,458)	(60)	(1,633)
Deferred contract revenues	(1,395)	(6,010)	(4,717)
Net cash used in operating activities	(23,186)	(48,088)	(34,750)
Investing activities:			
Short-term investments	(69,949)	13,492	17,455
Purchases of property, plant and equipment	(1,649)	(4,791)	(4,434)
Patent costs	(3,182)	(2,642)	(3,882)
Investments in affiliates	(20,599)	(14,233)	--
Net cash (used in) provided by investing activities	(95,379)	(8,174)	9,139
Financing activities:			
Net proceeds from issuance of equity	118,240	64,338	3,944
Proceeds from long-term borrowing	8,583	3,233	13,354
Principal payments on debt and capital lease obligations	(3,939)	(3,631)	(2,171)
Net cash provided by financing activities	122,884	63,940	15,127
Net increase (decrease) in cash and cash equivalents	4,319	7,678	(10,484)
Cash and cash equivalents at beginning of year	35,296	27,618	38,102
Cash and cash equivalents at end of year	$ 39,615	$ 35,296	$ 27,618
Supplemental disclosures of cash flow information:			
Interest paid	$ 3,454	$ 2,402	$ 3,191
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt and capital lease obligations for acquisitions of property, plant and equipment	$ 1,710	$ 2,071	$ 2,068
Additions to debt for patent acquisitions	$ --	$ --	$ 3,238
Additions to prepaids and other current assets from sale of equipment	$ 27	$ --	$ --

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 2000

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 No. 128, "Earnings per Share" ("SFAS 128"). Basic loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding during the period ("Basic EPS method"). Diluted earnings (loss) per common share is computed using the weighted-average number of common and dilutive common equivalent shares outstanding during the period ("Diluted EPS method"). Diluted common equivalent shares consist of shares issuable upon exercise of stock options and warrants and conversion of preferred stock. As Isis incurred a loss in the years ended December 31, 2000, 1999 and 1998, options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect would be antidilutive.

CONTRACT REVENUES AND EXPENSES

Contract revenues consist of non-refundable research and development funding and are recorded as earned based on the performance requirements of the collaborative research and development contracts. Contract fees for which no further performance obligations exist are recognized when the payments are received or when the collection is assured. Payments received in excess of amounts earned are recorded as deferred contract revenues. Research and development costs are expensed as incurred. For the years ended December 31, 2000, 1999 and 1998, costs and expenses of approximately $28,400,000, $26,000,000 and $35,000,000, respectively, were related to collaborative research and development arrangements.

REVENUE RECOGNITION

Isis recognizes revenue from product sales at the time of shipment. An estimate is made of the amount of the product that may be returned and current period sales are reduced accordingly. License fees consist of non-refundable fees from the sale of license rights to our proprietary technologies. Revenue from technology access fees, license fees and similar up-front payments will be deferred and recognized over the exclusivity period or term of the license or ongoing research period, as applicable, in accordance with Staff Accounting Bulletin No. 101.

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. The Company's securities are classified as "available-for-sale" in accordance with Statement of Financial Accounting Standards No. 115, "Accounting for Certain Investment in Debt and Equity Securities". These investments are carried at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal year. The cost of debt securities sold is based on the specific identification method. Gross realized gains and losses are included in interest income and have not been material. See Note 2 - Investments.

PROPERTY, PLANT AND EQUIPMENT

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

	DECEMBER 31, 2000	DECEMBER 31, 1999
Land	$ 1,163	$ 1,163
Buildings and improvements	18,495	16,911
Equipment	32,750	31,075
Furniture and fixtures	1,521	1,510
	53,929	50,659
Less accumulated depreciation	(31,304)	(26,714)
	$ 22,625	$ 23,945

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

Building	31.5 years
Improvements	15 years
Equipment	2.5-5 years
Furniture and fixtures	5 years

PATENT COSTS

Isis capitalizes certain costs related to patent applications, principally consisting of legal and filing fees. These costs are regularly reviewed to determine that they include costs for patent applications Isis is pursuing. Costs related to applications that are not being actively pursued are evaluated under Accounting Principles Board Statement 17, "Accounting for Intangible Assets" and are adjusted to an appropriate amortization period or immediately written-off if appropriate. Accumulated patent costs are amortized over their estimated economic lives of approximately 10 years, beginning with the date the patents are issued. The weighted average remaining life of issued patents was 7.6 years at December 31, 2000 and December 31, 1999. Accumulated amortization related to patents was $1,615,000 and $999,000 at December 31, 2000 and 1999, respectively.

INVESTMENT IN AFFILIATES

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

ORASENSE AND HEPASENSE

In April 1999, Isis and Elan Corporation, plc (Elan) formed Orasense, Ltd., a Bermuda limited company. In January 2000, Isis and Elan Corporation, plc formed HepaSense, Ltd., a Bermuda limited company. Each joint venture is owned 80.1% by Isis and 19.9% by Elan. While Isis owns 80.1% of the outstanding common stock of Orasense and HepaSense, Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in EITF 96-16. Therefore, Isis accounts for its investment in each joint venture under the equity method of accounting.

PANTHECO

During 2000, Isis entered into an agreement with Pantheco A/S ("Pantheco"), a Danish biotechnology company, in which Isis obtained a 22% equity position in Pantheco. The carrying value at December 31, 2000 was $840,000. Isis accounts for its investment in Pantheco under the equity method of accounting.

FAIR VALUE OF FINANCIAL INSTRUMENTS

The Company has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, short-term

borrowings, accounts payable, 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, 2000.

LONG-LIVED ASSETS

Isis follows Statement of Financial Accounting Standards (SFAS) No. 121, "Accounting for the Impairment of Long-Lived Assets and for Long-Lived Assets to be Disposed of" and evaluates long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying value of such assets or intangibles may not be recoverable. Recoverability of assets to be held and used is measured by comparison of the carrying amount of the asset to future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the assets. Assets to be disposed of are reported at the lower of the carrying amount or fair value less costs to sell.

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.

COMPREHENSIVE INCOME (LOSS)

Statement of Financial Accounting Standards (SFAS) 130, "Reporting Comprehensive Income" 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, 2000, 1999 and 1998 have been reflected in the Consolidated Statement of Stockholders' Equity (Deficit).

RECLASSIFICATION

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

IMPACT OF RECENTLY ISSUED ACCOUNTING STANDARDS

In March 2000, the Financial Accounting Standards Board issued FASB Interpretation ("FIN") No. 44, "Accounting for Certain Transactions Involving Stock Compensation--an Interpretation of APB Opinion No. 25." FIN 44 primarily clarifies (a) the definition of an employee for purposes of applying APB Opinion No. 25, (b) the criteria for determining whether a plan qualifies as a non-compensatory plan, (c) the accounting consequence of various modifications to the terms of previously fixed stock options or awards, and (d) the accounting for an exchange of stock compensation awards in a business combination. FIN 44 was effective July 1, 2000, but certain conclusions in FIN 44 cover specific events that occurred after either December 15, 1998 or January 12, 2000. In January 2000 Isis offered non-officer employees an opportunity to exchange certain of their existing stock options. These options are required to be accounted for as variable stock options in accordance with FIN 44. Variable stock options can result in significant increases and decreases in compensation expense subject to the variability of Isis' stock price.

In December 1999, the Securities and Exchange Commission (SEC) issued Staff Accounting Bulletin (SAB) No. 101, "Revenue Recognition in Financial Statements," which provides guidance on the recognition, presentation and disclosure of revenue in financial statements filed with the SEC. As amended, SAB 101, outlines the basic criteria that must be met in order to recognize revenue and provides guidance for disclosures related to revenue recognition policies, including revenue earned from collaborations between companies. The SEC deferred the implementation date of SAB 101 until the quarter ended December 31, 2000, with retroactive application to the beginning of the Company's calendar year. The Company believes that revenue recorded through December 31, 2000 complies with SAB 101.

2. INVESTMENTS

Isis invests its excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends in yields and interest rates. Isis has not experienced any material losses on its short-term investments. As of December 31, 2000, 73% of the debt securities held by Isis had a contractual maturity of one year or less, and the remaining 27% of the portfolio was due within 2 years.

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

	AVAILABLE-FOR-SALE SECURITIES (in thousands)		
	COST	GROSS UNREALIZED GAINS (LOSSES)	ESTIMATED FAIR VALUE
DECEMBER 31, 2000			
U.S. Treasury securities and obligations of U.S. Government agencies	$ 26,161	$ (14)	$ 26,147
U.S. corporate debt securities	61,360	140	61,500
Total debt securities	$ 87,521	$ 126	$ 87,647
DECEMBER 31, 1999			
U.S. Treasury securities and obligations of U.S. Government agencies	$ 7,311	$ (29)	$ 7,282
U.S. corporate debt securities	10,261	0	10,261
Total debt securities	$ 17,572	$ (29)	$ 17,543

3. LONG-TERM OBLIGATIONS AND COMMITMENTS

In 1996 and 1997, Isis borrowed a total of $22,576,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim International GmbH. The borrowed funds were used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and have ranged 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, 2000 and 1999 was $22,576,000, which approximated fair value.

In 1997, Isis obtained two term loans from a bank to refinance existing notes secured by real property and to fund facilities expansion. Both notes are secured by Isis' real property and bear interest at the prime interest rate (9.5% and 8.5% at December 31, 2000 and 1999, respectively) plus 0.5%. The first note in the amount of $3,707,000 requires monthly principal repayments of $12,433 plus interest with the remaining principal balance due in April 2002. The balance of this first note at December 31, 2000 and 1999 was $3,140,000 and $3,290,000, respectively. The second note in the amount of $6,000,000 requires monthly principal repayments of $50,000 plus related interest with the remaining principal balance due in July 2002. The balance at December 31, 2000 and 1999 was $3,900,000 and $4,500,000, respectively. As of December 31, 2000 and 1999, the carrying value of these variable rate long-term notes approximated fair value.

Between 1997 and 1998, Isis obtained a total of $40,060,000 in private debt financing. The terms of the financing provide for a ten year maturity on the debt, interest of 14% per annum and deferred interest

payments for the first five years of the loan. After the first five years, interest must be paid quarterly until the end of the loan, which is November 1, 2007. No principal repayments are required until the end of the loan. Because interest is deferred during the first five years, the principal balance will be $78 million on November 1, 2002. In conjunction with the debt financing, Isis issued warrants to purchase a total of 800,000 common stock shares to the lender, exercisable at $25 per share. The fair value of the warrants was estimated using the Black-Scholes option pricing model, with the following assumptions: expected life of 4.5 years, expected dividend yield of zero percent, expected volatility of 60 percent and a risk free interest rate of 5.9%. A total fair value of $5,426,000 was calculated for the warrants and was credited to equity. The allocation of value to the warrants creates an effective debt discount which is amortized using the effective interest method. The effective interest rate of this debt is approximately 16%, including the effect of the discount amortization. The debt of $57,995,000 and $49,086,000 at December 31, 2000 and 1999, respectively, is carried on the balance sheet net of accrued interest and the unamortized amount allocated to the warrants. The fair value of this debt at December 31, 2000 and 1999 approximated $60,479,000 and $52,000,000, respectively. The fair value of the long-term debt is estimated using discounted cash flow analyses, based on current borrowing rates for similar types of borrowing arrangements.

In December 1998, Isis purchased from Gilead Sciences, Inc. (Gilead), the holdings of Gilead's antisense patent estate. This acquisition included patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over three years. Isis has recorded the net present value of the future payments, using a discount rate of 10%. The balance of this obligation at December 31, 2000 and 1999 was $1,823,000 and $2,568,000, respectively, which approximated fair value.

In April 1999, Elan International Services (EIS) made available to Isis an $18.4 million line of credit under a convertible debt arrangement made in conjunction with the Orasense joint venture. The terms of the convertible debt provide interest at 12% per annum, compounded semi-annually, maturing April 19, 2005. No principal or interest payments are required until the end of the loan. The loan may be prepaid by the Isis at any time, at its option, in whole or in part, in cash or in common stock (at a price equal to the average market value of the common stock for the 60 trading days ending two business days prior to the date of prepayment). At any time prior to maturity, EIS may convert all or any portion of the loan outstanding, on a per tranche basis, into the number of shares of common stock obtained by dividing the amount to be converted by 150% of the average market value of the common stock for the 60 trading days ending two business days prior to the date of disbursement of such tranche. This debt facility is subordinate to the $40,000,000 private debt financing which matures November 2007. During 2000 and 1999, Isis borrowed $6,749,000 and $2,213,000, respectively, under this convertible debt agreement to provide development funding to Orasense. Based on the principal and accrued interest outstanding at December 31, 2000, the loan balance due at maturity will be $16,200,000, provided that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility as of December 31, 2000 and 1999 was $9,724,000 and $2,284,000, respectively, which approximated fair value.

In September 1999, Isis borrowed $1,019,000 from Abbott Laboratories, Inc. to be used by Isis as its contribution toward costs associated with Abbott's design and construction of a facility for commercial scale manufacturing of oligonucleotides. The terms of the financing provide for a two year maturity of the debt, with an annual interest rate of 2% over the Citibank prime rate calculated annually at the date of borrowing. The interest rate on this debt was 11.5% and 10.25% at December 31, 2000 and 1999, respectively. Interest is payable annually. The principal, which is due at maturity, can be paid in cash, common stock (based on 100% of the average closing price for the 20 trading days preceding loan maturity), or through increasing the price Isis would pay for the oligonucleotides produced by Abbott until the loan is repaid. The balance under this borrowing facility as of December 31, 2000 and 1999 was $1,019,000, which approximated fair value.

In January 2000, EIS made available to Isis a $12,000,000 line of credit under a convertible debt arrangement made in conjunction with the HepaSense joint venture. The terms of the convertible debt provide interest at 12% per annum, compounded semi-annually, maturing January 14, 2006. No principal or interest payments are required until the end of the loan. The loan may be prepaid by Isis at any time, at its option, in whole or in part, in cash or in common stock (at a price equal to 95% of the average market value of

the common stock for the 60 trading days ending two business days prior to the date of repayment); provided that no more than 50% of any prepayment amount shall be payable by the Company in the Company's common stock. At any time prior to maturity, EIS may convert all or any portion of the loan outstanding, on a per tranche basis, into the number of shares of common stock obtained by dividing the amount to be converted by 140% of the average market value of the common stock for the 60 trading days ending two business days prior to the date of disbursement of such tranche. This debt facility is subordinate to the $40,000,000 private debt financing which matures November 2007. During 2000, Isis borrowed $1,834,000 under this convertible debt agreement to provide development funding to HepaSense. Based on the principal and accrued interest outstanding at December 31, 2000, the loan balance due at maturity will be $3,400,000, providing that no prepayments or conversions occur prior to maturity. The balance under this borrowing facility as of December 31, 2000 was $1,856,000, which approximated fair value.

Annual debt maturities at December 31, 2000 are as follows (in thousands):

2001	$ 2,252
2002	7,310
2003	16,200
2004	6,376
2005	9,726
Thereafter	59,829
Total	$ 101,693

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through February 2007. 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, 2000 are as follows (in thousands):

	OPERATING LEASES	CAPITAL LEASES
2001	$ 2,143	$ 2,732
2002	1,967	1,801
2003	1,947	1,152
2004	1,722	104
2005	1,493	-
Thereafter	4,633	-
Total minimum payments	$ 13,905	$ 5,789
Less amount representing interest		(621)
Present value of future minimum payments		5,168
Less current portion		(2,355)
Long term portion		$ 2,813

Rent expense for the years ended December 31, 2000, 1999 and 1998 was $2,115,000, $1,736,000, and $1,760,000, respectively. Cost of equipment under capital leases at December 31, 2000 and 1999 was $9,754,000 and $8,394,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2000 and 1999 was approximately $5,425,000 and $4,633,000, respectively.

4. STOCKHOLDERS' EQUITY

PREFERRED STOCK

The Company is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. Preferred Stock consists of Series A and Series B Convertible Exchangeable 5% Preferred Stock and Series C Junior Participating Preferred Stock.

SERIES A CONVERTIBLE EXCHANGEABLE 5% PREFERRED STOCK

At December 31, 2000, Isis has 120,150 shares authorized, issued and outstanding of Series A Convertible Exchangeable 5% Preferred Stock. The shares have a term of six years and are convertible into Isis' common stock on or after March 31, 2002 at 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to March 31, 2002, or automatically in the event of a significant transaction, at 120% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to the transaction if the significant transaction occurs prior to March 31, 2002, or 125% if the significant transaction occurs thereafter. The Preferred Stock is exchangeable at the option of Elan at any time through and including June 30, 2002 for an incremental 30.1% of the issued and outstanding shares owned by Isis of Orasense. It also bears a mandatory pay-in-kind dividend of 5.0% per year based on the original issue price per share, compounded semi-annually payable only upon conversion into Isis' common stock or cash.

SERIES B CONVERTIBLE EXCHANGEABLE 5% PREFERRED STOCK

At December 31, 2000, Isis has 16,620 shares authorized, of which 12,015 shares are issued and outstanding of Series B Convertible Exchangeable 5% Preferred Stock. The shares have a term of six years and are convertible into Isis' common stock on or after June 30, 2002 at 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to June 30, 2002, or automatically in the event of a significant transaction, at 120% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to the transaction if the significant event occurs prior to June 30, 2002, or 125% if the significant transaction occurs on or after June 30, 2002. The Preferred Stock is also exchangeable for the ownership Isis holds in HepaSense. It also bears a mandatory pay-in-kind dividend of 5.0% per year based on the original issue price per share, compounded semi-annually payable only upon conversion into Isis' common stock or cash.

SERIES C JUNIOR PARTICIPATING PREFERRED STOCK

In December 2000, Isis adopted a Preferred Share Purchase Rights Plan (the "Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right (a "Right") for each outstanding share of Isis common stock, par value $0.001 per share (the "Common Shares"), held of record at the close of business on January 10, 2001. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group of 20 percent or more of Isis' common stock, the Rights permit the holders (other than the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share (the "Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share (the "Purchase Price"), subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and the qualifications, limitations and restrictions which make its value approximately equal to the value of a Common Share. Under certain conditions, the Rights may be redeemed by the Company's Board of Directors in whole, but not in part, at a price of $0.001 per Right.

COMMON STOCK

During the year ended December 31, 2000, Isis sold 4,442,465 shares of its common stock to institutional investors at negotiated prices ranging from $9.85 per share to $27.25 per share. In addition, during the year ended December 31, 2000, the Company sold 2,158,030 shares of its common stock to Ridgeway Investment Limited at prices ranging from $7.44 per share to $14.94 per share under the terms of the Common Stock Purchase Agreement. The per share average purchase prices reflect the average trading prices of the common stock over a period of time less a discount percentage ranging from 4.5% to 5.875%.

STOCK OPTION PLANS

1989 STOCK OPTION PLAN AND OTHER EMPLOYEE OPTION GRANTS

In June 1989 and as amended, Isis adopted a stock option plan which provides for the issuance of non-qualified 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, 2000, a total of 5,710,000 options were outstanding, options to purchase 3,414,000 shares were exercisable, and 849,000 shares were available for future grant. In fiscal year 1991 Isis granted 412,000 non-qualified stock options for common stock to certain individuals. At December 31, 2000, there were no options outstanding and 93,000 shares were available for future grant.

1992 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

In July 1992, Isis adopted the 1992 Non-Employee Directors' Stock Option Plan which provides for the issuance of non-qualified stock options for the purchase of up to 300,000 shares of common stock to Isis's non-employee directors. Options under this plan expire 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in four equal annual installments beginning one year after the date of grant. Options granted before January 1, 1996 vest over a five year period. At December 31, 2000, a total of 198,000 options were outstanding, 148,000 shares issued under this plan were exercisable and 61,000 shares were available for future grant.

2000 BROAD-BASED EQUITY INCENTIVE STOCK OPTION PLAN

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Stock Option Plan which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Under the 2000 plan, a total of 1,763,000 options were outstanding, 9,000 shares were exercisable, and 2,225,000 shares were available for future grant at December 31, 2000.

The following table summarizes stock option activity for the years ended December 31, 1998 through December 31, 2000 (in thousands, except per share data):

	NUMBER OF SHARES	PRICE PER SHARE			WEIGHTED AVG PRICE PER SHARE
Outstanding at December 31, 1997	6,442	$.14	to	$20.00	$ 9.80
Granted	1,168	$7.06	to	$15.44	
Exercised	(320)	$.14	to	$14.50	
Terminated	(304)	$3.75	to	$20.00	
Outstanding at December 31, 1998	6,986	$.14	to	$19.88	$10.27
Granted	1,539	$4.00	to	$18.00	
Exercised	(333)	$.14	to	$14.50	
Terminated	(490)	$3.88	to	$19.75	
Outstanding at December 31, 1999	7,702	$.43	to	$19.88	$10.68
Granted	4,069	$6.25	to	$17.69	
Exercised	(1,800)	$.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

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 12/31/00	WEIGHTED AVERAGE REMAINING CONTRACTUAL LIFE	WEIGHTED AVERAGE EXERCISE PRICE	NUMBER EXERCISABLE AS OF 12/31/00	WEIGHTED AVERAGE EXERCISE PRICE
$ 3.57 - $ 5.38	405	3.85	$ 4.16	404	$ 4.15
$ 5.50 - $ 6.88	3,473	6.64	$ 6.68	990	$ 6.40
$ 7.00 - $ 9.94	660	4.52	$ 8.92	479	$ 8.76
$10.00 - $10.94	559	8.43	$10.31	170	$10.34
$11.00 - $11.94	243	8.39	$11.50	78	$11.48
$12.00 - $12.94	1,474	7.42	$12.58	773	$12.54
$13.00 - $13.94	385	5.75	$13.21	330	$13.18
$14.00 - $17.88	292	6.50	$15.32	174	$15.58
$18.00 - $18.63	180	6.01	$18.07	173	$18.07
$ 3.57 - $18.63	7,671	6.58	$ 9.21	3,571	$ 9.73

EMPLOYEE STOCK PURCHASE PLAN

In 1991, the Board of Directors adopted and the stockholders subsequently approved, the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance thereunder. 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 offer or the end of each six-month purchase period. During 2000, 73,000 shares were issued under this plan to employees at prices ranging from $5.32 to $10.57 per share. At December 31, 2000, 341,000 shares were available for purchase under this plan.

STOCK-BASED EMPLOYEE COMPENSATION

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

	2000	1999	1998
Net loss - as reported	$ (54,699)	$ (59,645)	$ (42,983)
Net loss - pro forma	$ (63,110)	$ (69,446)	$ (49,761)
Basic net loss per share - as reported	$ (1.48)	$ (2.08)	$ (1.60)
Basic net loss per share - pro forma	$ (1.71)	$ (2.42)	$ (1.85)

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 2000: a risk-free interest rate of 6%; a dividend yield of 0%; a volatility factor of 80.0 % and an option life of 4.2 years; for 1999: a risk-free interest rate of 5.7%; a dividend yield of 0%; a volatility factor of 60.0 % and an option life of 3.7 years; and for 1998: a risk-free interest rate of 4.6%; a dividend yield of 0%; a volatility factor of 60.0 % and an option life of 4.1 years. The weighted average fair value of options granted was $7.81 for 2000, $6.41 for 1999, and 5.98 for 1998.

WARRANTS

In 1997 and 1998, Isis issued 500,000 and 300,000 warrants, respectively, in conjunction with a private debt financing agreement. As of December 31, 2000, all of the warrants remain outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3.

In 1999, Isis issued 215,000 warrants to Elan International Services, Ltd. as part of the joint venture collaboration between Isis and Elan to form Orasense, Ltd. As of December 31, 2000, all of the warrants remain outstanding at an exercise price of $24 per share. The warrants expire April 19, 2004.

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

As of December 31, 2000, total common shares reserved for future issuance was 8,402,000.

5. INCOME TAXES

Significant components of Isis' deferred tax assets as of December 31, 2000 and 1999 are shown below. Valuation allowances of $133,535,000 and $113,814,000 have been recognized for 2000 and 1999, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2000	1999
Deferred tax assets:		
Capitalized research expense	$ 10,856,000	$ 9,800,000
Net operating loss carryforwards	104,766,000	87,990,000
Research and development credits	17,351,000	13,910,000
Other, net	6,149,000	6,404,000
Total deferred tax assets	139,122,000	118,104,000
Deferred tax liabilities:		
Patent expense	(5,587,000)	(4,290,000)
Total deferred tax liabilities	(5,587,000)	(4,290,000)
Total net deferred tax assets	133,535,000	113,814,000
Valuation allowance for deferred tax assets	(133,535,000)	(113,814,000)
Net deferred tax assets	$ -	$ -

At December 31, 2000, approximately $16,273,000 of the valuation allowance for deferred tax assets relates to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2000, Isis had federal and California tax net operating loss carryforwards of approximately $295,543,000 and $29,645,000, respectively. Isis also had federal and California research credit carryforwards of approximately $13,226,000 and $6,346,000, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% limitation in the utilization of California loss carryforwards. The federal tax loss carryforward and the research credit carryforwards will begin expiring in 2004 unless previously utilized. Approximately $354,000 of the California tax loss carryforward expired during 2000 and the related deferred tax asset and tax loss carryforward amounts have been reduced accordingly. The remaining California tax loss carryforward will continue expiring in 2001, unless utilized.

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

6. RESEARCH AND DEVELOPMENT COLLABORATIVE ARRANGEMENTS AND LICENSING AGREEMENTS

In 1990, Isis entered into a collaborative agreement with Novartis to discover and investigate oligonucleotide compounds active against specific targets. In 1996, Isis and Novartis signed a definitive agreement broadening each company's antisense research and development collaboration to include the development of ISIS 3521 and ISIS 5132, anticancer compounds that were discovered through the research collaboration. The broadened collaboration also included research to discover additional therapeutic compounds. Under the terms of the expanded collaboration, Novartis funded the development of both ISIS 3521 and ISIS 5132. During 1999, Novartis concluded its participation in the development of ISIS 3521 and ISIS 5132, and as a result no further revenue was recognized in 2000. Included in the statement of operations for the years ended December 31, 1999 and 1998 are contract revenues arising from this collaboration totaling $7,527,000 and $15,641,000, respectively.

In July 1995, Isis and Boehringer Ingelheim International GmbH signed definitive agreements and formed a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2,000,000 shares of Isis's common stock for $28,500,000 in cash plus certain license rights. Boehringer Ingelheim and Isis provided equal funding for the combined research and development program, which came to a conclusion in December 1999. As a result, there was no related revenue included in the statement of operations for 2000. For the years ended December 31, 1999 and 1998, Isis recognized contract revenues of $6,974,000 and $6,544,000, respectively, from this collaboration.

In July 1997, Isis and Novartis Ophthalmics, formerly CIBA Vision Corporation, entered into an agreement granting Novartis Ophthalmics exclusive worldwide distribution rights for Vitravene-TM- (fomivirsen). Under the terms of the agreement, Isis will manufacture and sell Vitravene to Novartis Ophthalmics at a price that will allow Isis and Novartis Ophthalmics to share the commercial value of the product. Under the terms of the agreement, Novartis Ophthalmics is responsible for marketing and selling Vitravene worldwide and also for regulatory approvals outside of the United States and Europe. Additionally, Novartis Ophthalmics received the option to acquire the exclusive license to market and distribute a second generation antisense compound to treat CMV retinitis. At the inception of the agreement, Novartis Ophthalmics paid Isis a $5 million non-refundable pre-commercial fee to partially reimburse Isis for the costs incurred in discovering and developing Vitravene. That payment was recognized as revenue in 1997. In August 1998, the FDA approved Vitravene for marketing, and in the fourth quarter of the year Novartis Ophthalmics began selling Vitravene commercially. Since August 1998, Isis has recognized $674,000 in revenue related to shipments of Vitravene, which is included in the statement of operations under research and development revenues under collaborative agreements. Under the Novartis Ophthalmics agreement, Isis received a $2,500,000 milestone payment in each of 2000 and 1999, and earned contract revenue of $7,500,000 in 1998.

In June 1998, Isis entered into a research collaboration with Merck & Co. to discover small molecule drug candidates to treat patients infected with Hepatitis C virus (HCV). Isis and Merck will design, synthesize, and evaluate novel compounds that Merck will screen in its proprietary assays for identifying HCV replication inhibitors. Merck will commercialize drugs arising from the collaboration, and Isis retains the right to use technology developed in the collaboration in its antisense program. The three-year collaboration provides Isis with annual research support plus technology access fees, and milestone payments and royalties upon commercialization. The statement of operations for the years ended December 31, 2000, 1999 and 1998, reflects contract revenues of $3,000,000, $3,500,000 and $3,875,000, respectively, from Merck under the terms of this agreement.

In December 1998, Isis purchased from Gilead the holdings of Gilead's antisense patent estate. This acquisition included patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over three years. Isis made the initial $2,000,000 payment in December 1998, the second payment of $1,000,000 in December 1999 and the third payment of $1,000,000 in December 2000. Isis has recorded the net present value of the future payments as a long-term obligation on the balance sheet. The balance of this obligation

as of December 31, 2000 and 1999 was $1,823,000 and $2,568,000, respectively. Isis acquired the Gilead patents to enhance its dominant proprietary position in antisense technology. Isis also believes that the acquisition of the Gilead patents may reduce the risk of possible future patent infringement claims. Effort will be required by Isis' scientists to determine if the acquired patents can be used to develop potentially viable products.

In December 1998, Isis entered into a collaborative research agreement with AstraZeneca Pharmaceuticals to discover, develop and commercialize novel antisense-based cancer drugs. Under the terms of this collaboration, Isis will create and, with AstraZeneca, screen antisense-based candidates for certain cancer targets. The agreement specifies that Isis will receive a technology access fee and annual research funding during the first two years of the collaboration. The initial term of the research collaboration is three years with a clause that allowed AstraZeneca to terminate at the end of the second year. In December 2000, AstraZeneca terminated the agreement. The statement of operations for the years ended December 31, 2000 and 1999 each reflect contract revenues of $3,420,000 from AstraZeneca under the terms of this agreement.

Also in December 1998, Isis entered into a two-year research collaboration with Abbott Laboratories, Inc. to prioritize drug development targets using Isis' Antisense Target Validation Technology. The collaboration will enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Isis received from Abbott an up-front fee, and will receive quarterly research fees, milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. Isis will receive rights to Abbott genes to develop antisense drugs. The statement of operations for the years ended December 31, 2000 and 1999 reflects contract revenues of $1,000,000 and $1,250,000, respectively, from Abbott under the terms of this agreement.

In April 1999, Isis and Elan formed a joint venture to develop technology for the formulation of oral oligonucleotide drugs. The joint venture, Orasense, Ltd., is a Bermuda limited company which is currently owned 80.1% by Isis and 19.9% by Elan. Isis and Elan each contributed rights to certain oral drug delivery technology to the joint venture. In addition, Isis contributed rights to a proprietary oligonucleotide, which will be the first candidate for oral formulation by Orasense. Isis and Elan will provide development and manufacturing services to Orasense and will be entitled to royalties on milestone payments and royalties received by Orasense for development of orally formulated oligonucleotide drugs. If Isis enters into an agreement with Orasense for oral formulation of any Isis oligonucleotide drug, Isis will pay Orasense royalties and a portion of certain third party milestone payments with respect to the drug. In conjunction with this transaction, Isis sold 910,844 shares of Isis' common stock to Elan International Services (EIS) for $15,000,000, and issued a warrant to purchase up to 215,000 shares of Isis' common stock at $24 per share. The term of the warrant is five years. Isis also sold 120,150 shares of Isis' Series A Convertible Preferred Stock to EIS for $12,015,000 (See Note 4). For the years ended December 31, 2000 and 1999, Isis recorded $5,217,000 and $4,402,000, respectively, in revenue from Orasense. For the years ended December 31, 2000 and 1999, Isis recorded $9,702,000, and $7,242,000, respectively, as equity in the net loss of Orasense. Additionally, at December 31, 2000 and 1999, the balance sheet included $968,000 and $1,961,000, respectively, of contracts receivable relating to Orasense.

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

In January 2000, Isis and Elan formed a new joint venture to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus (HCV). This new joint venture, HepaSense Ltd., is a Bermuda limited company which is currently owned 80.1% by Isis and 19.9% by Elan. HepaSense plans to develop and commercialize this novel therapeutic for HCV, while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD-Registered Trademark- Drug Delivery System, a disposable subcutaneous infusion device. Isis and Elan have each licensed technology to HepaSense. Isis and Elan will provide development and manufacturing services to

HepaSense and will be entitled to royalties on any milestone payments and royalties received by HepaSense for development of HCV drugs. In conjunction with this transaction, Isis sold 297,619 shares of Isis' common stock to EIS for $7,500,000, and issued a warrant to purchase up to 14,881 shares of Isis' common stock at $50.40 per share. The term of the warrant is five years. Isis also sold 12,015 shares of Isis' Series B Convertible Preferred Stock to EIS for $12,015,000 (See Note 4). For the year ended December 31, 2000, Isis recorded $2,751,000 in revenue from HepaSense, and recorded $6,237,000 as equity in the net loss of HepaSense. Additionally, at December 31, 2000, the balance sheet included $481,000 of contracts receivable relating to HepaSense.

In June 2000, Ibis Therapeutics, a division of Isis and Agouron Pharmaceuticals, Inc., a Pfizer Company (Pfizer), entered into a collaboration for the discovery and development of small molecule drugs against certain RNA targets in an undisclosed therapeutic area. Using Ibis' proprietary technology and Pfizer's expertise in small molecule drug discovery, the collaboration focuses on discovering drugs that bind to RNA. Pfizer will fund collaborative research, pay an up-front technology access fee and make milestone payments totaling up to $37 million for the first product. In addition, Pfizer will develop and commercialize drugs discovered by the collaboration and will pay Isis royalties on the sales of drugs. For the year ended December 31, 2000, Isis recorded $2,393,000 in total contract revenues from Pfizer.

In August 2000, GeneTrove-TM-, a division of Isis, initiated an antisense target validation collaboration with the R.W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies, to assess and prioritize genes as drug discovery targets. GeneTrove will use its proprietary antisense technology to assist Johnson & Johnson to study the function and therapeutic relevance of novel gene targets. Johnson & Johnson will make milestone payments for the successful validation of such novel gene targets. For the year ended December 31, 2000, Isis recorded $255,000 in total contract revenues from Johnson & Johnson.

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

In September 2000, Isis entered into an agreement to license its novel antisense chemistry, Peptide Nucleic Acid (PNA), to Pantheco A/S (Pantheco), a Danish biotechnology company, on a nonexclusive basis to treat diabetes and cardiovascular diseases. Pantheco completed a financing to raise funds to support its current business and to fund this expansion of therapeutic focus in October 2000. Isis received 40,000 shares of Pantheco common stock valued at $1.1 million based on Pantheco's recent financing as consideration for the license agreement. In addition, Pantheco will pay Isis royalties and milestones on products developed using the PNA. This is the second license of PNA technology from Isis to Pantheco. As part of the first licensing transaction completed in November 1998, Isis received an equity position in Pantheco for which no carrying value was given as realization of the value of the equity interest in Pantheco was uncertain. As a result of the current transaction, Isis' ownership of Pantheco is approximately 22%. For the year ended December 31, 2000, Isis recorded $285,000 as equity in the net loss of Pantheco.

7. RESTRUCTURING

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

departments of the Company. For the year ended December 31, 2000, the Company incurred total restructuring costs of $1.6 million.

8. EMPLOYEE POSTEMPLOYMENT BENEFITS

Isis has an employee 401(k) salary deferral plan, covering all domestic employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($10,500 for 2000). The Company has not made any matching contributions into the plan as of December 31, 2000.

9. AFFILIATE SUPPLEMENTARY DISCLOSURE

ORASENSE

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounts for its investment in Orasense under the equity method of accounting. The following table presents summary financial information (in thousands, except per share amounts) for Orasense, Ltd. as of and for the year ended December 31:

	2000	1999
BALANCE SHEET:		
Assets		
Cash and cash equivalents	$ 10	$ 6
In-license costs, net	6,250	11,250
Total assets	$ 6,260	$ 11,256
Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ 1,216	$ 2,534
Other current liabilities	8	-
Common stock, $1.00 par value; 12,000 Authorized, issued and outstanding at December 31, 2000 and 1999	12	12
Additional paid-in capital	26,177	17,751
Accumulated deficit	(21,153)	(9,041)
Total liabilities and stockholders' equity	$ 6,260	$ 11,256
RESULTS OF OPERATIONS:		
Revenues	$ -	$ -
Research and development expenses	7,112	5,290
Amortization of acquired license	5,000	3,751
Total operating expenses	12,112	9,041
Net loss	$ (12,112)	$ (9,041)

HEPASENSE

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounts for its investment in HepaSense under the equity method of accounting. The following table presents summary financial information (in thousands, except per share amounts) for HepaSense, Ltd. as of and for the year ended December 31, 2000.

	2000
BALANCE SHEET:	
Assets	
Cash and cash equivalents	$ 1
In-license costs, net	10,000
Total assets	$ 10,001
Liabilities and Stockholders' Equity	
Amounts due to affiliates	$ 488
Other current liabilities	9
Common stock, $1.00 par value; 6,001 shares authorized, issued and outstanding at December 31, 2000	6
Series A Preferred stock, $1,250 par value; 6,000 shares authorized, issued and outstanding at December 31, 2000	7,500
Additional paid-in capital	9,784
Accumulated deficit	(7,786)
Total liabilities and stockholders' equity	$ 10,001
RESULTS OF OPERATIONS:	
Revenues	$ -
Research and development expenses	2,786
Amortization of acquired license	5,000
Total operating expenses	7,786
Net loss	$ (7,786)

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

	MAR. 31	JUN. 30	SEP. 30	DEC. 31
2000 QUARTER ENDED				
Revenues	$ 4,054	$ 6,985	$ 18,280	$ 7,936
Operating expenses	16,671	15,160	18,661	17,388
Loss from operations	(12,617)	(8,175)	(381)	(9,452)
Net loss	(18,327)	(14,302)	(5,409)	(15,447)
Accretion of dividends on preferred stock	(281)	(306)	(311)	(316)
Net loss applicable to common stock	$ (18,608)	$ (14,608)	$ (5,720)	$ (15,763)
Basic and diluted net loss per share (1)	$ (0.56)	$ (0.40)	$ (0.15)	$ (0.40)

	MAR. 31	JUN. 30	SEP. 30	DEC. 31
1999 QUARTER ENDED				
Revenues	$ 6,576	$ 7,208	$ 10,638	$ 9,503
Operating expenses	17,131	19,205	18,679	21,969
Loss from operations	(10,555)	(11,997)	(8,041)	(12,466)
Net loss	(12,604)	(16,523)	(12,430)	(17,668)
Accretion of dividends on preferred stock	-	(117)	(150)	(153)
Net loss applicable to common stock	$ (12,604)	$ (16,640)	$ (12,580)	$ (17,821)
Basic diluted net loss per share (1)	$ (0.46)	$ (0.59)	$ (0.44)	$ (0.58)

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

EXHIBIT 10.4

Optionee: STANLEY T. CROOKE Date: JANUARY 6, 2000

ISIS PHARMACEUTICALS, INC.
SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: 250,000

VESTING SCHEDULE:

NUMBER OF SHARES (INSTALLMENT)	DATE OF EARLIEST EXERCISE (VESTING)
250,000	01/02/2002*

*This option shall fully vest on January 2, 2006; provided, however, that this option will fully vest on January 2, 2002, if and only if, the following objectives are met: (1) as of December 31, 2000, the amount of cash available to the Company is greater than $40 million; (2) the Company reaches a "go/no go" decision on four product opportunities (indications); (3) the restructuring of the Company, as described in the Restructuring Plan is successful; and (4) the Company has completed at least one new corporate partnership.

Exercise Price Per Share: $6.81(1) Expiration Date: 1/05/2010(2)

Isis Pharmaceuticals, Inc.

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

Optionee: _____
Address: 3211 Piragua Street
Encinitas, CA 92024

OPTIONEE:

1. Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and

2. Acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the undersigned optionee and the Company and its affiliates regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject with the exception of the following agreements only:

None: _____ Other: _____
(Initial)

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

Optionee: B. LYNNE PARSHALL Date: JANUARY 6, 2000

ISIS PHARMACEUTICALS, INC.
SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: 170,000

VESTING SCHEDULE:

NUMBER OF SHARES (INSTALLMENT)	DATE OF EARLIEST EXERCISE (VESTING)
170,000	01/02/2002*

*This option shall fully vest on January 2, 2006; provided, however, that this option will fully vest on January 2, 2002, if and only if, the following objectives are met: (1) as of December 31, 2000, the amount of cash available to the Company is greater than $40 million; (2) the Company reaches a "go/no go" decision on four product opportunities (indications); (3) the restructuring of the Company, as described in the Restructuring Plan is successful; and (4) the Company has completed at least one new corporate partnership.

Exercise Price Per Share: $6.81(1) Expiration Date: 1/05/2010(2)

Isis Pharmaceuticals, Inc.

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

Optionee: _____
Address: 2645 Marmol Court
Carlsbad, CA 92009

OPTIONEE:

1. Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and

2. Acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the undersigned optionee and the Company and its affiliates regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject with the exception of the following agreements only:

None: _____ Other: _____
(Initial)

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

Optionee: DEBBY JO BLANK Date: JANUARY 6, 2000

ISIS PHARMACEUTICALS, INC.
SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: 100,000

VESTING SCHEDULE:

NUMBER OF SHARES (INSTALLMENT)	DATE OF EARLIEST EXERCISE (VESTING)
100,000	01/02/2002*

*This option shall fully vest on January 2, 2006; provided, however, that this option will fully vest on January 2, 2002, if and only if, the following objectives are met: (1) as of December 31, 2000, the amount of cash available to the Company is greater than $40 million; (2) the Company reaches a "go/no go" decision on four product opportunities (indications); (3) the restructuring of the Company, as described in the Restructuring Plan is successful; and (4) the Company has completed at least one new corporate partnership.

Exercise Price Per Share: $6.81(1) Expiration Date: 1/05/2010(2)

Isis Pharmaceuticals, Inc.

By: Optionee:

Duly authorized on behalf of the Board of Directors

Address: 318 Colima Court
La Jolla, CA 92037

OPTIONEE:

1. Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and

2. Acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the undersigned optionee and the Company and its affiliates regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject with the exception of the following agreements only:

None: Other:

(Initial)

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

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-3 and Form S-8) of Isis Pharmaceuticals, Inc. of our report dated February 2, 2001 with respect to the financial statements of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2000.

/s/ ERNST & YOUNG LLP

San Diego, California
February 27, 2001