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, 1999
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 [ ]

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 [ ]

The approximate aggregate market value of the 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 $533,724,000 as of March 24, 2000.*

The number of shares of common stock outstanding as of March 24, 2000 was 35,094,199.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Registrant's definitive Proxy Statement which will be filed on or before April 24, 2000 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on June 8, 2000 is incorporated by reference into Part III of this Report.

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* Excludes 4,265,360 shares of common stock held by directors and officers and stockholders whose beneficial ownership exceeds 10 percent of the shares outstanding at February 25, 2000. 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

Isis Pharmaceuticals, Inc. is a leading genomics-based drug discovery and development company that is focused on RNA. Our goal is to create important new drug discovery technology platforms that will improve the productivity of the pharmaceutical industry and will enable our discovery and development of important new drugs to treat disease and improve the lives of patients. RNA is a novel target for drug discovery, and Isis has established a dominant position in RNA research. 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 and Ibis, a robust pipeline of drugs in development and genomics services.

Our technologies have reached a level of maturity to be of substantial value to the company and to industry partners. Additionally, our technologies are protected by a broad patent estate covering inventions in areas such as antisense chemistries, gene sequences, antisense drugs in specific diseases and manufacturing methods.

ANTISENSE. Our leading technology, antisense, is a science based on the direct application of gene sequence information. We have pioneered and reduced to practice the synthesis of antisense inhibitors to the RNA of genes. Antisense inhibitors can be used directly as drugs or as genomics tools. Based on the specificity of antisense, we believe we can design antisense drugs that are safer and more effective than traditional drugs. We have succeeded in bringing the first antisense drug to market, Vitravene(TM), for CMV retinitis. Our development pipeline includes five compounds presently in clinical trials, of which at least one will advance to Phase III before year-end. We have successfully leveraged our antisense technology through corporate collaborations with Elan Corporation, Merck & Co., Astra-Zeneca PLC, Abbott Laboratories, Inc., Aventis S.A. (formerly Rhone-Poulenc Rorer), CIBA Vision, Novartis Pharma AG and Boehringer Ingelheim International GmbH. These collaborations increase our financial resources, improve our technological strength and establish valuable development and commercial relationships.

GENETROVE(TM) GENOMICS. In the company's GeneTrove division, we are leveraging our antisense expertise to provide pharmaceutical and biotechnology companies gene function and target validation information about genes that they are interested in targeting for drug development. We can provide this information rapidly and efficiently for partners with the proprietary methods and systems that we have developed for our own use in creating antisense inhibitors as drugs, because the scientific process is identical. We have collaborations in place with three major pharmaceutical partners for these services and plan to grow this business in the near term.

IBIS THERAPEUTICS(TM) TECHNOLOGY. With recently acquired knowledge of RNA structures and new sequence data from the gene sequence ("genomic") databases, Isis is developing a new drug discovery paradigm: specific targeting of RNA with small molecule drugs. We are creating and using new software to identify particular RNA structures to serve as targets for drugs. Our proprietary molecular modeling techniques can be used to predict the shape of drug binding pockets in 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 anti-bacterials, and we believe that the technology will be useful in a broad range of diseases.

ANTISENSE RESEARCH, DRUG DISCOVERY, DEVELOPMENT AND MANUFACTURING

Antisense research involves the following process: We identify a target gene, learn its precise genetic sequence, or code, and then assemble a synthetic strand of genetic code to complement the code of its RNA precisely. The product we've created, the synthetic strand of DNA, is called an antisense inhibitor to the target gene. Antisense inhibitors can be used in two ways: 1) directly as a drug, because production of a disease-

causing protein is prevented when the inhibitor binds to the gene and 2) as a tool to understand a gene's function and value as a drug target.

Our antisense drug research programs focus on targets associated with infectious, inflammatory, cardiovascular and metabolic diseases and cancer. Our expertise in molecular biology and drug discovery enables rapid identification of potent antisense inhibitors of disease causing proteins. We are then able to specifically tailor the inhibitor to the particular disease indication targeted through our medicinal chemistry expertise. Additionally, our medicinal chemistry programs have developed novel chemistries that allow us to design new antisense compounds that are potentially safer and more active than current antisense drugs and which have the potential to allow more convenient forms of dosing, including oral delivery.

In 1998, the U.S. Food and Drug Administration approved Vitravene(TM) (fomivirsen) to treat CMV retinitis in AIDS patients. Vitravene(TM) is the first antisense drug to be approved for marketing. CIBA Vision, our distribution partner for this drug, launched Vitravene(TM) in November 1998. CIBA Vision is the eye care unit of life sciences leader Novartis Pharma AG. In 1999, Vitravene(TM) also received marketing approval in Europe and Brazil. We currently have five antisense compounds in human clinical trials, with additional compounds arising out of our broad research program in preclinical development which are represented in the chart below:

ISIS DEVELOPMENT PIPELINE

[GRAPH]

ISIS 3521 is a potent, selective inhibitor of protein kinase C (PKC) - -(alpha) gene expression that has demonstrated encouraging results in Phase I trials. Phase II trials are being conducted in patients with a range of solid tumors.

ISIS 5132, is a potent selective inhibitor of C-raf kinase. Phase II trials are being conducted in patients with a range of solid tumors.

ISIS 2503 is a potent, selective antisense inhibitor of Ha-ras in Phase II clinical trials in patients with a variety of solid tumors.

ISIS 2302 inhibits expression of intercellular adhesion molecule 1 (ICAM-1), a molecule involved in a variety of inflammatory diseases and conditions. ISIS 2302 is in Phase IIa trials of a topical formulation for psoriasis and an enema formulation for ulcerative colitis.

ISIS 14803 is an antisense inhibitor of the Hepatitis C Virus that is in Phase I/II clinical trials in patients with chronic Hepatitis C.

ISIS 104838 is an inhibitor of inflammatory target TNF-(alpha) which is involved in diseases such as rheumatoid arthritis and Crohn's disease.

ISIS 107248 is an inhibitor of CD49d, which is involved in inflammatory diseases such as multiple sclerosis.

We have successfully leveraged our technology through supportive corporate collaborations with Elan Corporation, Merck & Co., AstraZeneca PLC, Abbott Laboratories, Inc., CIBA Vision, Novartis Pharma AG and Boehringer Ingelheim International GmbH. These collaborations increase our financial resources, improve our technological strength and establish valuable development and commercial relationships. As a result, we have been able, and expect to continue, to pursue drug discovery and development activities aggressively. We have retained substantial commercial rights to all of our drug candidates, including those funded by corporate collaborators.

Isis has established a very strong patent position to cover its diverse portfolio of inventions and intellectual property. As of February 28, 2000 we have been issued or allowed more than 590 patents worldwide. A particularly important patent covering RNase H1, the key enzyme responsible for the mechanism of action of antisense gene inhibition, was issued to Isis in December 1999. This important patent will significantly strengthen the dominant position of Isis in both antisense therapeutics and genomics.

We have focused significant efforts on developing cost-effective, large-scale, Good Manufacturing Practices manufacturing capability for antisense compounds. We currently manufacture antisense compounds to meet all of our research and clinical needs, as well as the needs of our partners. We have achieved significant manufacturing cost reductions through chemistry and process improvements. We believe that, with reasonably anticipated benefits resulting from increases in scale, we will be able to manufacture antisense compounds at commercially attractive prices. Under the terms of our agreement with CIBA Vision, Isis manufactures all of the commercial supplies of Vitravene(TM).

In December 1999, the unexpected failure of our pivotal clinical trial of ISIS 2302 in Crohn's disease prompted the restructuring of the company. In January 2000, we announced a restructuring plan to reduce expenses and focus resources on the development of antisense drugs with significant commercial potential. In conjunction with this restructuring, we will reduce Isis' workforce by approximately 140 employees in the first four months of 2000. We estimate that the costs associated with this restructuring will approximate $2 million. Under the restructuring plan, Isis will have cash and committed funds sufficient to support activities for at least three years. We expect to make significant progress toward our primary goals of commercializing antisense drugs, creating value from both our Ibis and GeneTrove divisions, and building shareholder value in that time frame.

GENETROVE(TM) DIVISION - ANTISENSE TARGET VALIDATION AND GENE FUNCTIONALIZATION

Our GeneTrove division uses antisense as a tool to provide vital information about human genes: what they do, how they behave within cells and biological systems, whether they are important in disease, whether they would make good drug targets. The processes involved in answering these questions are called gene functionalization and target validation. We have created and/or integrated proprietary systems to functionalize and validate gene targets in a highly efficient manner, as these processes are fundamental to our core research in identifying antisense drug candidates.

We are also performing these genomics services for three pharmaceutical company partners. Our collaboration with Abbott Laboratories began in 1998, with Aventis S.A. (formerly Rhone-Poulenc Rorer) began in 1999 and with Astra-Zeneca in 2000. With the windfall 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 drug development candidates. We intend to grow our GeneTrove business this year by marketing the speed, accuracy and efficiency of our genomics capabilities to new partners.

IBIS DIVISION - RNA SMALL MOLECULE DRUG DISCOVERY

Through the development of antisense technology, we have amassed expertise in RNA structure and function. We have combined this understanding with innovations in medicinal chemistry, bioinformatics, comparative genomics, and mass spectrometry to develop a novel proprietary drug discovery program that

targets the structured regions of RNA as the binding site for small molecule drugs. In this program we have developed proprietary technologies to:

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

2) Predict structure of RNA from genome sequence data;

3) Quickly create and screen large libraries of small molecule compounds designed to bind RNA; and

4) Screen for RNA-binding molecules using novel mass spectrometry. As an example of the power of this technology, we expect to be able to screen 10,000 compounds against 10 RNA targets per day.

While our initial area of focus is in discovering novel antibacterial drugs, we believe the Ibis technology has potential in cancer, central nervous system disease, inflammation and degenerative diseases of aging. To date, we have funded the Ibis program through grants from the Defense Advanced Research Projects Agency. The technology has now reached an appropriate level of maturity to enable us to market it to potential pharmaceutical industry partners, and we plan to grow this business by establishing new collaborations.

ISIS DRUG DISCOVERY AND DEVELOPMENT

Isis' efforts as a drug discovery and development company have focused on RNA. RNA is a novel target for drug discovery, and Isis has established a dominant position in RNA research. We have assembled a team of world-class scientists whose expertise in molecular and cellular biology, medicinal chemistry, RNA biochemistry, bioinformatics and pharmacology has been centered on RNA. When our knowledge in these core disciplines is combined with our clinical development capabilities, we have an integrated platform from which to develop of important new drugs to treat disease and improve the lives of patients. Our work in RNA-based drug discovery and development work has produced two important drug-discovery technologies: antisense and Ibis RNA-targeted small molecule discovery. From these technologies we have developed a robust pipeline of promising new drugs and efficient genomics tools that unlock value from gene sequence data.

ANTISENSE TECHNOLOGY PLATFORM

ANTISENSE DRUG DISCOVERY

Almost all human diseases are a result of inappropriate protein production or performance. 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 development because it targets disease-causing proteins before they are produced. Antisense drugs can be designed to treat a wide range of diseases, including infectious, inflammatory and cardiovascular diseases and cancer.

Antisense technology represents a new model for drug discovery because it focuses on compounds that interact with messenger RNA or mRNA, which has not been a site for traditional drug interaction. Using the information contained in mRNA, we design chemical structures, easily recognized by the body, which resemble mRNA and DNA. These potent "antisense" oligonucleotides inhibit the production of disease-causing proteins. This method of drug design is highly productive, and in ten years we have created a substantial pipeline of drug candidates, including 5 compounds currently in clinical trials.

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 the cost

of manufacturing them. In the ten years since our founding, we have made significant progress in understanding and using antisense technology to create drugs, and have established a leadership position in this field.

THE MECHANISM OF ANTISENSE DRUGS

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 more than 100,000 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 is to be performed. 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 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 information encoded in a single mRNA is then translated into many copies of the sequence of amino acids that builds the protein.

Antisense drugs are mirror or complementary images of small segments of mRNA. To create antisense drugs, nucleotides are linked together in short chains called oligonucleotides. Each antisense drug is designed to bind to a specific sequence of nucleotides in its mRNA target to inhibit production of the protein encoded by the target mRNA. 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 do not act until after the disease causing protein has been produced.

Antisense drugs can be designed to be much more selective than traditional drugs. Because antisense drugs interact by binding to mRNA and not, as traditional drugs do, by binding to proteins, 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. 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. As a result of this unique selectivity, antisense drugs have the potential to be far less toxic than traditional drugs because they can be designed to minimize the impact on unintended targets.

ISIS' GENETROVE(TM) DIVISION

ANTISENSE 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 almost completed. The next steps in the process of making drugs and creating value from genomics are to identify the functions of the 100,000 plus human genes (gene functionalization) and to identify which genes are good targets for drugs (target validation). While this is a challenging task, Isis has developed its GeneTrove division, responsible for the company's antisense target validation and gene functionalization program that can provide this genomic information in an efficient and cost effective manner.

GeneTrove's antisense target validation and gene functionalization program is based on Isis' expertise in producing highly specific antisense inhibitors to genes and on a variety of specialized technology that the company has 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 100 gene targets per year. We are filing patent applications on these gene targets as rapidly as they can be produced, thus expanding our proprietary position in gene function and antisense.

- Comparative genomics and covariance analysis, fields that Isis has pioneered, provide key insights into biological function and pathways. The process involves the comparison of molecules and molecular systems of different organisms to find similarities and differences across species. By determining how the molecules of biological systems co-vary, we gain insights about how the component parts of complex systems fit together. By assessing the evolutionary position at which genes become expressed or diverge, genes can be placed in likely pathways and we can achieve a great deal of understanding about gene function.

- Low-density DNA arrays developed by GeneTrove use proprietary chemistry. When used in parallel with commercial arrays, GeneTrove can acquire unique data, including insights regarding gene function in normal and disease processes and can also identify potential toxicological problems associated with modulation of a particular gene.

- A proprietary bioinformatics database, called MetaGraph, is capable of assimilating vast quantities of genomics data and finding relationships in complex data arrays.

GeneTrove has already achieved many significant accomplishments. With a relatively small-scale effort, Isis has identified antisense inhibitors to more than 500 genes, patented many of these findings and expects to create antisense inhibitors to all important human genes over the next several years. As inhibitors to these genes are created and tested, the data are being incorporated into our pathway-oriented genomic database. To date, over 20 pathways have been characterized, including: MAP-kinases, apoptosis, NF-Kappa B, cell adhesion, and TNF signaling and insulin signaling. We have established Isis' first three target validation and gene functionalization partnerships with Abbott Laboratories, Aventis and AstraZenca and we are pursuing additional partnerships.

IBIS TECHNOLOGY PLATFORM

RNA-TARGETED SMALL MOLECULE DRUG DISCOVERY

Ibis Therapeutics is our program to discover low molecular weight, potentially orally bioavailable drugs that work by binding to RNA. Ibis leverages 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:

- Mining genomes for structured RNA in therapeutic targets;

- Predicting the three-dimensional structure of RNA from genome sequence data and designing RNA-targeted small molecules;

- Synthesizing libraries of compounds designed to find RNA; and

- Screening for RNA-binding molecules using novel massively parallel screening technology and producing lead compounds for further optimization and development.

With Ibis, we are developing and integrating genome mining software to identify these 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 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 10 RNA targets.

Our initial area of focus in Ibis is discovering novel antibacterial compounds. The technology has potential application in cancer, central nervous system disease, inflammation, as well as degenerative diseases of aging. To date, we have funded Ibis through government sponsored grants from the Defense Advanced Research Projects Agency and the National Institute of Standards and Technology. Our goal for Ibis is for it to be self-funding through corporate partner support. We will move Ibis toward this goal by providing drug candidates for development and providing optimized leads to pharmaceutical partners for development and commercialization.

PRODUCTS APPROVED AND UNDER DEVELOPMENT

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

ISIS PRODUCTS IN DEVELOPMENT

COMPOUND	TARGET	DISEASE INDICATION	DEVELOPMENT STATUS(1)	COMMERCIAL RIGHTS
Vitravene (fomivirsen)	CMV	Cytomegalovirus Retinitis	Approved for marketing in the U.S., Europe and Brazil. Other market applications under review.	Isis/CIBA Vision(2)
ISIS 3521	PKC-(alpha)	Cancer	Phase II	Isis
ISIS 5132	C-raf kinase	Cancer	Phase II	Isis
ISIS 2503	Ha-ras	Cancer	Phase II	Isis
ISIS 2302	ICAM-1	Psoriasis (topical)	Phase II	Isis
		Ulcerative colitis (enema)	Phase II	
ISIS 14803	HCV	Hepatitis C	Phase I/II	HepaSense, Ltd.(3)
ISIS 104838	TNF-(alpha)	Inflammation	IND Candidate	Isis/ Orasense, Ltd.(4)
ISIS 107248	CD49d	Inflammation	IND Candidate	Isis

(1) An "IND candidate" is a compound for which IND-enabling toxicology and pharmacokinetic studies have been initiated and IND preparation has begun.

(2) CIBA Vision has the exclusive right to distribute fomivirsen.

(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.

We also have a significant research program with the potential to yield additional development candidates in the future. As described in the section of this report entitled "Risk Factors - Uncertainties

Associated with Clinical Trials," the product candidates listed in the preceding table may not progress beyond their current status or yield a commercially viable product.

INFECTIOUS DISEASES

CYTOMEGALOVIRUS (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, retinitis caused by CMV 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 three years, this has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections including CMV. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet, cidofovir and fomivirsen. Foscarnet and cidofovir are available in intravenous (IV) dosing forms only. Ganciclovir is available in IV and oral doses, as well as in an intraocular implant form.

VITRAVENE(TM) (FOMIVIRSEN). In August 1998, the FDA approved Vitravene(TM) to treat CMV retinitis in AIDS patients. Vitravene(TM) is an antisense compound discovered by Isis. CIBA Vision, our worldwide distribution partner for this drug, launched Vitravene(TM) in November 1998. CIBA Vision is a subsidiary of Novartis Pharma AG. See "Collaborative Agreements - CIBA Vision." In 1999 Vitravene(TM) also received marketing approval in Europe and Brazil. We delivered our first commercial shipment of Vitravene(TM) to our partner CIBA Vision in 1998, earning product revenue of $560,000 in that year. No commercial shipments of Vitravene(TM) were made in 1999, and no product revenue was earned.

HEPATITIS C (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 are expected to die from this disease each year. Interferon-a therapy, used alone or in combination with 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 toxicities.

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. Under a joint venture agreement signed in January 2000, ISIS 14803 is being co-developed with Elan Corporation, a leader in the area of drug delivery.

A Phase I/II clinical study of ISIS 14803 began in early 2000. This study will evaluate safety and efficacy. Patients in this Phase I/II trial will receive ISIS 14803 intravenously 3 times a week for 4 weeks. Studies of the subcutaneous delivery of ISIS 14803 are also planned. Subsequently, studies of ISIS 14803 using Elan's MEDIPAD, a minimally invasive microinfusion pump, will be initiated.

CANCER

Much of our work in the area of cancer is focused 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 can be effective 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 II 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. 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 the isotype believed to be involved in abnormal cell growth without inhibiting the isotypes required for healthy cells to grow.

ISIS 3521 is nearing the completion of Phase II clinical trials as an anticancer agent, both alone and in combination with traditional cancer chemotherapies. The Phase II trials are studying the effect of this drug in treating a variety of cancer tumors. This compound inhibits protein kinase C-(alpha), or PKC-(alpha), a protein associated with abnormal cell growth. Based on promising data from a Phase I/II study, we plan to initiate Phase III clinical trials of ISIS 3521 for patients with non-small cell lung cancer in late 2000. Results from the Phase I/II trial show that of 17 patients with non-small cell lung cancer, 15 have benefitted from the drug. Eleven of the 17 patients (65%) have experienced partial responses. One patient had a minor response and 3 patients had stable disease lasting 4 to 8 months. Only 4 of 17 patients have died, with the longest survival being 23 months following study entry. With a median of 10 months of follow-up, 77% of the patients are alive and continuing to be evaluated.

In Phase I and Phase II studies, ISIS 3521 stabilized disease, reduced tumor mass and reduced tumor markers in patients with lung cancer, ovarian cancer and lymphoma. In those trials, ISIS 3521 caused no significant side effects. In a Phase II study of ISIS 3521 as a single agent in the treatment of patients with refractory non-Hodgkin's lymphoma, 1 of 7 patients treated so far has had a partial response and one other is too early to evaluate.

The Phase I studies included 56 patients with various types of cancer that had not responded to standard treatment. In these Phase I trials, the drug was well-tolerated by patients with no significant side effects. We also saw preliminary evidence of anticancer activity.

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 by inhibiting expression of ras genes in cell culture and animal models. ISIS 2503 has also inhibited the growth of multiple different human cancers in nude mouse xenograft models.

In Phase I studies, ISIS 2503 was well-tolerated, with no clinically significant toxicities observed among 22 patients with a variety of solid tumors who received the drug by 14-day continuous infusion repeated every 21 days. Prolonged stable disease was observed in 4 patients on this trial, including one patient with pancreatic cancer who had disease stabilization for 8 treatment courses administered over 6 months.

In Phase II trials of ISIS 2503, the compound is being evaluated 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. ISIS 2503 has been well-tolerated, with no clinically significant toxicities observed among patients with a variety of solid tumors. A Phase I trial of ISIS 2503 plus gemcitabine has been completed and will be followed by 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.

ISIS 5132 is in Phase II clinical trials as an anticancer agent. The Phase II trials are studying the effect of this drug in treating a variety of cancer tumors. 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 clinically significant side effects. A trial in ovarian cancer has not yet been completed. There are no current plans to develop this drug further in the other tumor types that have been studied (prostate cancer, colon cancer, non-small cell lung cancer). Several patients in this trial experienced disease stabilization.

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 ("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 has been demonstrated 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 a cause of these disorders, ICAM-1 is thought to contribute to the pathology of these diseases and conditions. We have identified lead compounds for other adhesion molecules including CD49d (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) (TNF-(alpha)), interleukin 5 (IL-5) and the IL-5 receptor. Lead antisense compounds targeting 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 in five disease indications: 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. Approximately 400,000 people in North America and a similar number in Europe are afflicted with Crohn's disease. Based on the positive results of a Phase II study, we decided to initiate a pivotal quality trial of ISIS 2302 in Crohn's disease. That 300 patient trial was completed in December 1999. The data from that clinical trial did not demonstrate efficacy and the profile of the drug did not support an NDA filing. The efficacy demonstrated, using the combined primary end point of clinical remission plus complete steroid withdrawal, was approximately 20% in all three arms of the study. This negative outcome was unexpected. In late 1998, the company conducted an interim analysis of the first 150 patients enrolled in the study. Based on the positive data from the interim analysis, the company believed that the 300 patient study was likely to support an NDA filing.

  In the trial, the effects of two weeks and four weeks of treatment with ISIS 2302 were compared to placebo. The analysis of the data from the study failed to demonstrate the same efficacy profile of ISIS 2302 seen in the interim analysis. At the interim analysis, ISIS 2302 induced steroid-free complete clinical remissions in 29% of the drug-treated patients versus a placebo response rate of 14%.

This was statistically different (p=0.047). Both the 2- and 4-week dose groups had similar results. In the placebo group, 34% of the patients discontinued from the study prematurely because of lack of response, while only 16% of the ISIS 2302 patients discontinued early. This also was statistically significant (p=0.020). Other measures of efficacy also favored ISIS 2302 in the interim analysis.

In the second half of the study, the results were significantly different than the interim analysis. Only 12% of the ISIS 2302 treated patients enrolled in the second half of the study achieved steroid-free remission. This differs from the results in the initial 150 patients (p=0.0047). In the second half of the study, only 6% of the placebo patients discontinued from the study prematurely because of lack of response. This differed significantly from the results in the first half of the study (p=0.0004). In contrast, the early discontinuation rate for lack of clinical response in the drug treated arms was 20%, not significantly different from the results in the first 150 patients. The safety database has not yet been fully analyzed; however, the drug was well tolerated. The second half of the trial differs statistically from the first half in every meaningful parameter. We are in the process of determining if we can identify those factors that contributed to the differences between the two halves of the study.

- PSORIASIS. In early 2000, we initiated Phase II trials of ISIS 2302 for psoriasis as a topical cream formulation. 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 shown to be safe and effective would represent a significant improvement in treatment for patients and a significant commercial opportunity.

- KIDNEY TRANSPLANT REJECTION. The Phase II study in kidney transplant rejection, which has been proceeding at a pace mandated by the regulatory authorities as they carefully monitor clinical studies in this patient population, is nearing completion. 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 will also limit our investment in the development of ISIS 2302 as an enema formulation for treatment of ulcerative colitis.

- RHEUMATOID ARTHRITIS. We completed the Phase II study in rheumatoid arthritis. We saw evidence of therapeutic activity. ISIS 2302 was well tolerated, and the safety profile of the drug continues to be attractive. Based on this outcome, we are pursuing development of a second-generation, orally active antisense inhibitor of ICAM-1 in lieu of continuing development of ISIS 2302 in rheumatoid arthritis. We continue to believe that inhibition of ICAM-1 is a promising anti-inflammatory strategy in rheumatoid arthritis and will continue to test second-generation inhibitors of this target for this disease.

ISIS 104838. ISIS 104838 is a second-generation antisense inhibitor of TNF-(alpha). This compound has shown promising results in models of inflammatory disease. In clinical trials it will be evaluated as a possible treatment for a variety of inflammatory diseases including rheumatoid arthritis and Crohn's disease. We are preparing to file an IND for ISIS 104838 and plan to initiate Phase I clinical studies in the first half of 2001. An oral formulation of ISIS 104838 is being developed co-developed with Elan under our Orasense joint venture.

ISIS 107248. ISIS 107248 is a second-generation antisense inhibitor of CD49d (VLA-4). This compound, which will be evaluated as a possible treatment for a variety of inflammatory diseases including multiple sclerosis, is currently undergoing preclinical toxicology and pharmacokinetic studies. We are preparing to file an IND for ISIS 107248 and plan to initiate Phase I clinical studies in 2001.

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, Ibis and GeneTrove 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, Ibis and GeneTrove 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.

COLLABORATIVE 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.

ELAN - HEPATITIS C

In January 2000, Isis and Elan Corporation agreed to form a new subsidiary of Isis to develop an antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus (HCV). The new subsidiary is called HepaSense and will develop and commercialize this novel therapeutic for HCV while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD(R) 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. ISIS 14803 began Phase I clinical trials in early 2000.

Isis and Elan have each licensed significant technology to HepaSense. As part of the transaction, Elan will purchase $7.5 million of Isis Common Stock in April 2000 and may purchase an additional $7.5 million of common stock upon completion of a mutually agreed milestone. Both investments will be at a premium to Isis' market price. Elan also purchased Isis Series B Preferred Stock which will be convertible in the future into either Isis stock or stock in HepaSense. In addition, Elan will make available to Isis a $12.0 million line of credit for Isis' funding commitment to HepaSense.

ISIS 14803 is an antisense drug that inhibits HCV replication. In preclinical studies, ISIS 14803 demonstrated specific reduction of the HCV RNA expression in both cell cultures and mouse model systems. A Phase I/II clinical study of ISIS 14803 began in early 2000. This study will evaluate safety and efficacy. Patients in this Phase I/II trial will receive ISIS 14803 intravenously 3 times a week for 4 weeks. Studies of the subcutaneous delivery of ISIS 14803 are also planned. Subsequently, Isis will initiate studies of ISIS 14803 using Elan's MEDIPAD. Elan's proprietary subcutaneous MEDIPAD(R) 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(R) System.

ELAN - ORAL FORMULATION

In April 1999, Isis and Elan formed a new subsidiary to develop a platform technology for the oral delivery of antisense drugs. Isis is the majority shareholder in this new subsidiary, named Orasense. The first oral drug Orasense is working on is ISIS 104838, Isis' antisense inhibitor of tumor necrosis factor - (alpha) (TNF-(alpha)). TNF-(alpha) is a gene that has been implicated in a wide range of inflammatory diseases.

Elan made a $27 million equity investment in Isis, 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 Isis or in Orasense.

Isis has 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 size and charge 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 PLC to discover, develop and commercialize novel antisense drugs targeting specific genes associated with cancer. In this collaboration, we are creating antisense candidates and are working together with AstraZeneca to optimize them. AstraZeneca will develop drugs arising out of the collaboration. AstraZeneca will pay us technology access fees and provide research funding as well as milestone payments and royalties for any drugs progressing into clinical development and onto the market. The initial term of this collaboration is three years. In 1998, AstraZeneca paid $2 million in technology access fees. In 1999, AstraZeneca paid $2.9 million for research support and fees. While the initial focus of this collaboration is on a limited number of cancer targets, we can, with AstraZeneca, also pursue additional targets in cancer and expand the collaboration to targets in other therapeutic areas. The agreement also provides that the collaboration can also be extended beyond its initial term.

MERCK

In June 1998, we established a research collaboration with Merck & Co. to discover small molecule drug candidates to treat patients infected with Hepatitis C virus. Our chemists, working together with Merck scientists, will design, synthesize and evaluate novel compounds that Merck will screen in its proprietary enzymatic assays for identifying Hepatitis C virus replication inhibitors. Merck will 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 and milestone payments and royalties upon commercialization. In 1998 and 1999, we received $3.9 million and $2.5 million, respectively, from Merck under the terms of this agreement.

CIBA VISION

In 1997, we entered into an agreement with CIBA Vision, granting it exclusive worldwide distribution rights for Vitravene(TM). Under the terms of the agreement, we will receive $20 million in pre-commercial fees and milestones. As of December 31, 1999, we have received a total of $15 million of these pre-commercial fees and milestones. While CIBA Vision will market and sell Vitravene(TM) worldwide, we will manufacture and sell Vitravene(TM) to CIBA Vision, at a price that will allow us to share the commercial value of the product with CIBA Vision. The FDA approved Vitravene(TM) for commercial marketing in August 1998. In 1999 Vitravene(TM) received marketing approval in Europe and Brazil. We delivered our first commercial shipment of Vitravene(TM) to our partner CIBA Vision in 1998, earning product revenue of $560,000. No commercial shipments of Vitravene(TM) were made in 1999, and no product revenue was earned. See "Products Under Development - Cytomegalovirus (CMV) Retinitis."

BOEHRINGER INGELHEIM

In 1995, we and Boehringer Ingelheim formed an alliance to combine the clinical development and research programs of both companies in the field of cell adhesion. The collaboration supported the clinical development of ISIS 2302 in a number of different diseases, and the discovery of both small molecule and antisense inhibitors to various novel call adhesion targets. In 1999, we reacquired ISIS 2302 from Boehringer Ingelheim. Under the terms of the renegotiated agreement, Isis has sole responsibility for the development and commercialization of ISIS 2302 and other antisense inhibitors of cell adhesion molecules discovered during the collaboration. Boehringer Ingelheim will receive a royalty on the commercial sales of these antisense drugs. Boehringer Ingelheim now has sole responsibility for the development and commercialization of any small molecule inhibitors of cell adhesion molecules discovered during the collaboration, with Isis receiving a royalty on the commercial sales of these small molecule drugs.

In addition to funding one-half of the collaboration's research and development, Boehringer Ingelheim made additional investments in ISIS and provided us with a line of credit. As of December 31, 1999, outstanding borrowings under this line of credit totaled $ 22.6 million. The line of credit is no longer available for additional borrowing.

ISIS 2302 is in Phase II clinical trials for psoriasis, ulcerative colitis and renal transplant rejection. We are also evaluating data from a Phase III study of ISIS 2302 in Crohn's disease to determine if further development is warranted. See "Products Under Development - Inflammatory Diseases."

As of February 25, 2000, Boehringer Ingelheim owned approximately 8% of our outstanding Common Stock.

NOVARTIS

We began our research and development collaboration with Novartis (then called Ciba-Geigy Limited) in 1990. The research portion of the collaboration ended in September 1998, having produced two drugs currently in development, ISIS 3521 and ISIS 5132. Novartis funded the clinical development of ISIS 3521 and ISIS 5132 through Phase II. In late 1999, Novartis chose to conclude its participation in the development of ISIS 3521 and ISIS 5132 at the completion of the current Phase II clinical trials. See "Products Under Development - Cancer - ISIS 3521; -- ISIS 5132." As of February 25, 2000, Novartis owned approximately 7% of our outstanding Common Stock.

GENETROVE ANTISENSE TARGET VALIDATION AND GENE FUNCTIONALIZATION COLLABORATIONS

With the entire human genome expected to be sequenced by the year 2003, identification and understanding of those genes that play a key role in disease will become increasingly important to pharmaceutical companies to develop of novel drugs. Antisense technology can be used to provide functional data on the importance of a specific gene in causing or maintaining a disease. Antisense technology uses genetic sequence information to rapidly design inhibitors of any gene target. Because of their exquisite specificity, antisense inhibitors can inhibit the selected gene only, without an impact on other closely related genes. As a result, antisense inhibitors allow the identification of function of that single gene target more precisely than any other method.

GeneTrove, Isis' antisense target validation and gene functionalization program, provides genomic information with unsurpassed productivity and efficiency to pharmaceutical companies. Using the proprietary chemistries and systems developed by Isis, we can move from in vitro analysis to animal model in one step and provide solutions to our partner's queries within weeks. GeneTrove's capabilities are validated by our accomplishments. GeneTrove has identified antisense inhibitors to more than 500 genes and we have patented many of these findings. In addition, we have characterized over 20 pathways, including: MAP-kinases, apoptosis, NF-Kappa B, cell adhesion, and TNF signaling and insulin signaling. We have also validated more than 20 gene targets in animal models. Importantly, our technology has been embraced by three major pharmaceutical partners, which are using our capabilities to help evaluate, select and prioritize genes as potential drug targets.

ASTRAZENECA

In January 2000, we entered into a target validation collaboration with AstraZeneca. The collaboration will use our target validation technology to assess and prioritize genes identified within AstraZeneca's genomics programs. This collaboration will enable AstraZeneca to determine the function and therapeutic value of 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. The initial term of this collaboration is three years.

AVENTIS

In September 1999, we entered into a target validation collaboration with Aventis (formerly Rhone-Poulenc Rorer). The collaboration will use our target validation technology to assess genes identified within Aventis' genomics programs. This collaboration will enable RPR 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. The initial term of this collaboration is three years. RPR will pay Isis research fees and milestone payments based on the success of the program. We received payments totaling $613,000 in 1999.

ABBOTT LABORATORIES

In December 1998, we entered into a target validation collaboration with Abbott Laboratories, Inc. The collaboration utilizes our target validation technology to enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Abbott will pay us an upfront fee, research fees, and milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. We will also receive rights to develop drugs targeting Abbott proprietary genes for Abbott. The initial term of this collaboration is two years. We received payments totaling $250,000 in 1998 and $1 million in 1999.

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 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 greatly 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.

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. Access to an alternate manufacturing source will provide 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 Isis' 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 February 28, 2000, we have been issued or allowed more than 590 patents worldwide and have filed more than 532 patent applications in the United States and counterparts of many of these applications in other countries. Patents issued 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 messenger RNA target sequences, which cover our rights to the genetic sequences that our compounds target;

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

- Method claims for the manufacture of oligonucleotides, which cover our new, improved 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.

In December 1999 Isis was issued U.S Patent 6,001,653, covering Human RNase H1. RNase H1 is a cellular enzyme that degrades RNA when antisense drugs bind to RNA. Most antisense inhibitors work through this mechanism of action and it has proven to be the most potent and broadly useful mechanism of action for antisense inhibitors used as drugs and as tools in target validation. Our patent covers the DNA sequence for Human RNase H1, methods of making any antisense inhibitor or drug using the RNase H1 mechanism, and methods of screening to identify effective antisense inhibitors of genes that use RNase H1.

We believe the RNase H1 patent has the potential to benefit Isis in many ways. It solidifies our dominance in antisense technology by further strengthening our vast patent estate. It also enhances our attractiveness as a partner for both therapeutic research collaborations and for genomic collaborations. In addition, we anticipate that this patent will produce significant revenues for the company in the form of licensing fees.

We have obtained licenses from various parties that we deem to be necessary or desirable for the manufacture, use or sale of our products. These licenses (both exclusive and non-exclusive) generally require us to pay royalties to the parties on product sales. We may not be able to obtain licenses to other required technology or, if obtainable, such technology may not be available at reasonable cost. Our failure to obtain a license to any technology required to commercialize our products may have a material adverse impact on our business.

We consider that in the aggregate our issued patents, patent applications and licenses under patents owned by third parties are important to our success. The patent positions of pharmaceutical, biopharmaceutical and biotechnology firms are generally uncertain and involve complex legal and factual questions. Consequently, even though we are currently pursuing patent applications with the U.S. and foreign patent offices, we do not know whether any of the pending applications will result in the issuance of any additional patents or whether any issued patents will provide significant proprietary protection or will be circumvented or invalidated. Litigation, which could result in substantial cost to us, may also be necessary to enforce any patents issued to us or to determine the scope and validity of others' proprietary rights in court or in administrative proceedings. In addition, to determine the priority of inventions, we may find it necessary to participate in interference proceedings declared by the U. S. Patent and Trademark Office or in opposition, nullity or other proceedings before foreign agencies with respect to any of our existing or future patents or patent applications, which could result in substantial cost to us. We may find it necessary to participate, at substantial cost, in International Trade Commission proceedings to abate importation of goods that would compete unfairly with our products.

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. Obtaining approval from the FDA and other regulatory authorities for a new therapeutic may take several years and involve substantial expenditures. Moreover, ongoing compliance with these requirements can require the expenditure of substantial resources. Difficulties or unanticipated costs may be encountered by us or our licensees or marketing partners in their respective efforts to secure necessary governmental approvals, which could delay or preclude us or our licensees or marketing partners from marketing their products. In conjunction with obtaining approval of Vitravene(TM), we successfully passed the manufacturing pre-approval inspection by the FDA. Approval of each new therapeutic 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.

Vitravene(TM) 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.

The development by others of new treatments for the diseases for which we are developing compounds could render our compounds non-competitive or obsolete. Furthermore, because of the fundamental differences between antisense and other technologies, there may be applications for which the products of one technology are superior to those of another. We are aware of several companies with late-stage compounds in development for diseases we are pursuing.

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 February 25, 2000, we employed 352 individuals. After the restructuring is completed in the first four months of 2000, we expect to employ approximately 276 individuals, of whom 87 hold advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. We believe that we have been highly successful in attracting skilled and experienced scientific personnel; however, competition for such personnel is intensifying. None of our employees is covered by collective bargaining agreements, and management considers relations with its employees to be good.

EXECUTIVE OFFICERS

The executive officers of the Company and their ages as of February 29, 2000 are as follows:

STANLEY T. CROOKE, M.D., Ph.D....54
Chairman of the Board, President and Chief Executive Officer

Dr. Crooke was a founder of the Company and has been its Chief Executive Officer and a director since January 1989 and has served as President since February 1999. He was elected Chairman of the Board in February 1991. Dr. Crooke previously served as President of the Company from January 1989 to May 1994. From 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, most recently as President of Research and Development of SmithKline & French Laboratories. Dr. Crooke is a director of Valentis, Inc., Idun Pharmaceuticals, Inc., and 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....44
Executive Vice President, Chief Financial Officer and Secretary

Ms. Parshall has served as Executive Vice President since December 1995, Chief Financial Officer of the Company since June 1994, and Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of the Company, and from November 1991 to February 1993, she was a Vice President of the Company. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP, counsel to the Company, 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.

DEBBY JO BLANK, M.D....48
Executive Vice President

Dr. Blank joined Isis in March 1999 as Executive Vice President. Prior to joining the Company, she was the President and Chief Operating Officer of Cypress Bioscience, Inc. from 1996 to 1999. She also held various senior management positions at Advanced Technology Laboratories, Syntex Laboratories, Inc., The DuPont Merck Pharmaceutical Company, and E.I. DuPont & Company.

C. FRANK BENNETT, Ph.D.....43
Vice President, Biology

Dr. Bennett has served as 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 the Molecular and Cellular Biology department. Prior to joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions.

DAVID J. ECKER, Ph.D.....45
Vice President & Managing Director, Ibis Therapeutics

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

and as 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.

PATRICIA LOWENSTAM....53
Vice President, Human Resources

Ms. Lowenstam has served as Vice President, Human Resources since January 1995. She joined Isis in August 1992 as 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.

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, 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 cannot guarantee that we will 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(TM). We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products. We expect to have ongoing discussions with the FDA and foreign regulatory agencies with respect to all of our drugs in clinical development.

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(TM), a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. We delivered our first commercial shipment of Vitravene(TM) to our partner CIBA Vision in 1998, earning product revenue of $560,000. No commercial shipments of Vitravene(TM) were made in 1999, and no product revenue was earned.

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, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will 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.

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 FURTHER 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 in designing drugs that work at the genetic level to block the production of disease-causing proteins.

In late 1999, we completed a Phase III trial of ISIS 2302 in Crohn's disease. The data from that study did not demonstrate efficacy and did not support an NDA filing. This negative outcome was unexpected. In late 1998, the company conducted an interim analysis of the first 150 patients enrolled in the study. Based on the positive data from the interim analysis, the company believed that the 300 patient study was likely to support an NDA filing. This same result could occur with other products under development.

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 Isis was founded in January 1989. As of December 31, 1999, our accumulated losses were approximately $257 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(TM). This product has limited sales potential relative to most pharmaceutical products. 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 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 market acceptance of Vitravene(TM);
- 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.

If we find that we do not have enough money, additional funds will need to be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be 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. 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.

In 1998, we entered into an antisense oligonucleotide manufacturing collaboration with Avecia Life Science Molecules of Manchester, England pursuant to which Avecia LSM will supply a portion of our requirements of drugs for clinical trials. As of the date of this report, we have not yet received any supply of drugs under this arrangement, and we cannot guarantee that Avecia LSM will prove to be an acceptable alternative supplier.

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 have been developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time 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, we cannot assure you that patents will be granted on any of our patent applications in the United States or in other countries. We also cannot assure you that the scope of any of our issued patents will be sufficiently broad to offer meaningful protection. In addition, 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.

To date, we have not experienced any patent or other intellectual property litigation. However, we cannot guarantee that we will not 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 such 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 to 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 stiff 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 last twelve months, the market price of our common stock has ranged from $4 per share to $39 per share. The market price can be affected by many factors, including, for example, fluctuation in our operating results, announcements of 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 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 the 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, 15% or more of our voting stockholders, 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 the outstanding common stock. These provisions may discourage certain types of transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of the stockholders to approve transactions that they think may be in their best interests. In addition, the 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 GMP manufacturing suite) in five buildings located on our "campus" in Carlsbad, California. Three of these buildings are owned by Isis and, as of December 31, 1999, secure approximately $7.8 million in indebtedness of the Company. Two of the buildings are leased 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. We believe that our facilities will be adequate to meet our needs through 2000.

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 the 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
1998		
First Quarter	$ 16.06	$12.00
Second Quarter	$ 16.25	$11.63
Third Quarter	$ 16.00	$ 7.00
Fourth Quarter	$ 13.31	$ 8.88
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

As of January 31, 2000, there were approximately 1,278 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 April 20, 1999, in conjunction with the formation of the Orasense joint venture, Isis sold 120,150 shares of Isis' Series A Convertible Preferred Stock to Elan International Services for $12,015,000. In conjunction with this transaction, Isis also sold 910,844 shares of Isis' Common Stock to EIS for $15,000,000, and issued to EIS a warrant to purchase up to 215,000 shares of Isis' Common Stock at $24 per share. The term of the warrant is 5 years. We expect that the proceeds from the sale of these securities will be used for general

corporate purposes, including, but not limited to, funding the research and development activities of the Orasense joint venture.

At any time after March 31, 2002, the Preferred Stock (including accrued dividends) will be convertible at EIS' option into shares of Isis' Common Stock at 125% of the 60-trading day average closing price of Isis' common Stock ending two business days prior to March 31, 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 until June 30, 2002, the holders of Preferred Stock may exchange their Preferred Stock with Isis for common shares of Orasense held by Isis that represent 30.1% of the total outstanding capital stock of Orasense. The exchange right will terminate if the Preferred Stock is converted into Isis' Common Stock, unless such conversion occurs as a result of a liquidation or certain transactions involving a change of control of Isis.

Until March 31, 2002, EIS will, at Isis' request, purchase convertible debt of Isis in an amount equal to Isis' share of budgeted funding for Orasense. The convertible debt will have a term of six years, bear interest at the rate of 12% and be convertible into Isis' Common Stock at a premium. Isis may prepay the convertible debt in cash or in Isis' Common Stock. Isis will use the proceeds of the sale of the convertible debt to provide additional development funding to Orasense.

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,				
	1999	1998	1997	1996	1995
STATEMENT OF OPERATIONS DATA:					
Research and development revenues	$ 33,925	$ 38,611	$ 32,722	$ 22,663	$ 12,966
Research and development expenses	66,413	62,200	55,940	45,653	33,175
Net loss applicable to common stock	(59,645)	(42,983)	(31,066)	(26,521)	(23,712)
Basic and diluted net loss per share	(2.08)	(1.60)	(1.17)	(1.04)	(1.10)
Shares used in computing basic and diluted net loss per share	28,703	26,873	26,456	25,585	21,514

	DECEMBER 31,				
	1999	1998	1997	1996	1995
BALANCE SHEET DATA:					
Cash, cash equivalents and short-term investments	$ 52,839	$ 58,848	$ 86,786	$ 77,624	$ 77,407
Working capital	44,213	40,651	62,573	56,300	60,040
Total assets	103,107	96,074	117,881	101,305	99,569
Long-term debt and capital lease obligations, less current portion	87,254	77,724	56,452	19,864	4,714
Accumulated deficit	(256,761)	(197,116)	(154,133)	(123,067)	(96,546)
Stockholders' equity (deficit)	869	(4,186)	34,852	58,385	75,850

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

Since its inception in January 1989, almost all of Isis' 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 the next several years. Our revenue comes from collaborative research and development agreements with pharmaceutical companies, 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 Agreements." In 1998, we received approval from the U.S. Food and Drug Administration ("FDA") to begin marketing our first product, Vitravene(TM), a drug used to treat CMV retinitis.

RESULTS OF OPERATIONS

Years Ended December 31, 1999 and December 31, 1998

Our revenue from collaborative research and development agreements was $33.9 million for the year ended December 31, 1999, compared with $38.6 million in 1998, a decrease of 12%. 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. We delivered our first commercial shipment of Vitravene(TM) to our partner CIBA Vision in 1998, earning product revenue of $560,000. No commercial shipments of Vitravene(TM) were made in 1999, and no product revenue was earned.

In April 1999, Isis and Elan Corporation formed a joint venture to develop a platform technology for the oral delivery of antisense drugs. The joint venture, Orasense Ltd. is a Bermuda limited company. While Isis owns 80.1% of the outstanding common stock of Orasense, Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in EITF 96-16. Therefore, Isis does not consolidate the financial statements of Orasense, but instead accounts for its investment in Orasense under the equity method of accounting. During 1999, Isis recognized $4.4 million in contract revenue for research and development activities performed for Orasense.

Research and development expenses rose 7% to $66.4 million in 1999 from $62.2 million in 1998. The increase in research and development expenses occurred because compounds in preclinical and clinical development continued to advance into more expensive stages of development. We expect that research and development expenses will decrease from the 1999 levels as the company implements the restructuring plan announced in January 2000. 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 and support of our increasing research and development efforts. We expect that general and administrative expenses will decrease from the 1999 levels as the company implements its restructuring plan.

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 for five years. Therefore, of the $11.4 million interest expense in 1999, $8.1 million was accrued under the long-term debt agreements and will not require current cash payment.

Our net loss 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 Isis' equity in the loss of Orasense. Isis' loss from operations was $43.1 million in 1999, compared to $37.8 million in 1998. We expect that operating losses will be

reduced from the 1999 level, as we implement our restructuring plan. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

At December 31, 1999, our net operating loss carryforward for federal income tax purposes was approximately $246 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 $11 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 Isis.

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

Years Ended December 31, 1998 and December 31, 1997

Our revenue from collaborative research and development agreements was $38.6 million in 1998 and $32.7 million in 1997, an increase of 18%. The receipt of $5 million from CpG ImmunoPharmaceuticals, Inc. for a license to certain issued patents together with $1.8 million in from a research collaboration with Merck contributed to this revenue increase. We delivered our first commercial shipment of Vitravene(TM) in 1998, earning product revenue of $0.6 million.

Research and development expenses amounted to $62.2 million in 1998 and $55.9 million in 1997. This increase in research and development expenses resulted from Isis' growing preclinical and clinical development activities.

Operating expenses also included $5.2 million related to the write-off of acquired patents.

General and administrative expenses were $9.5 million in 1998, compared with $8.1 million in 1997. This increase was due to expanded business development and investor relations activities and support of our increasing research and development efforts.

Interest expense increased to $9.4 million in 1998 from $3.6 million in 1997. This increase was due to borrowing a total of $40 million in the fourth quarter of 1997 and the second quarter of 1998. This borrowing was under the terms of ten-year private debt financings.

Our net loss was $43.0 million, or $1.60 per share, in 1998 and $31.1 million, or $1.17 per share, in 1997.

LIQUIDITY AND CAPITAL RESOURCES

We have financed our operations with revenue from contract research and development, by selling equity securities and by issuing long-term debt. From our inception through December 31, 1999, we have earned approximately $180 million in revenue from contract research and development. We have also raised net proceeds of approximately $250 million from the sale of equity securities since Isis was founded. We have borrowed approximately $72 million under long-term debt arrangements to finance a portion of our operations.

As of December 31, 1999, we had cash, cash equivalents and short-term investments of $52.8 million and working capital of $44.2 million. In comparison, we had cash, cash equivalents and short-term investments of $58.8 million and working capital of $40.7 million as of December 31, 1998. This decrease in cash and short-term investments resulted from the funding of operating losses, investments in capital equipment and building improvements, investment in the Orasense Ltd. joint venture and principal payments on debt and capital lease obligations. This decrease was offset in part by the sale of $15 million of common stock and $12 million of convertible preferred stock to Elan Corporation in conjunction with the Orasense joint venture. Other sources

of funding in 1999 included $37.3 million from our issuance of common stock and $3.2 million from long term debt financing.

The agreement with Elan International Services Ltd. provides us with access to up to $18.4 million in convertible debt. This debt is to be used to support the Orasense joint venture collaboration. Restrictions on the availability of the debt facility are based on the anticipated collaboration costs and the amount of funds available to us. As of December 31, 1999, the outstanding balance under this line of credit was $2.3 million. 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, 1999 was $49,086,000. See Note 3 to the Financial Statements, "Long-term obligations and commitments".

As of December 31, 1999, our long-term obligations (including current portion) totaled $91.1 million, compared to $81.3 million at December 31, 1998. 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, committed contract revenue and committed equity funding will be sufficient to meet our anticipated requirements for at least three years.

IMPACT OF YEAR 2000 COMPUTER ISSUES

In 1998 and 1999 SEC filings, the Company discussed the nature and progress of its plans to become Year 2000 ready. In late 1999, the Company completed its remediation and testing of systems. As a result of those planning and implementation efforts, the Company experienced no significant disruptions in mission critical information technology and non-information technology systems and believes those systems successfully responded to the Year 2000 date change. The Company expensed approximately $150,000 during 1999 in connection with remediating its systems. The Company is not aware of any material problems resulting from Year 2000 issues, either with its products, its internal systems, or the products and services of third parties. The Company will continue to monitor its mission critical computer applications and those of its suppliers and vendors throughout the year 2000 to ensure that any latent Year 2000 matters that may arise are addressed promptly.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

The Company is exposed to changes in interest rates primarily from its long-term debt arrangements and, secondarily, its investments in certain short-term investments. The Company invests its excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. The Company does 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, the Company believes that, while the securities the Company holds are subject to changes in the financial standing of the issuer of such securities, the Company is not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

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

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

Not applicable.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS

The information required by this item (with respect to Directors) is incorporated by reference from the information under the caption "Election of Directors" contained in our definitive Proxy Statement (the "Proxy Statement") which will be filed on or before April 24, 2000 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2000 Annual Meeting of stockholders to be held on June 8, 2000.

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 36 of this Report.

(A)(2) INDEX TO FINANCIAL STATEMENT SCHEDULES

None required.

(A)(3) INDEX TO EXHIBITS

See Index to Exhibits on pages 33 through 35.

The following management compensatory plans and arrangements are required to be filed as exhibits to this Report pursuant to Item 14(c):

EXHIBIT NUMBER		DESCRIPTION
10.2	--	Registrant's 1989 Stock Option Plan, as amended.(5)
10.3	--	Revised form of Incentive Stock Option Agreement under the 1989 Stock Option Plan.(2)
10.4	--	Revised form of Supplemental Stock Option Agreement under the 1989 Stock Option Plan.(2)
10.5	--	Form of Incentive Stock Option Agreement dated January 1, 1995 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.(3)
10.6	--	Form of Supplemental Stock Option Agreement dated January 1, 1995 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.(3)
10.7	--	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended.(2)
10.8	--	Revised form of Supplemental Stock Option Agreement under Registrant's 1992 Non-Employee Directors' Stock Option Plan.(4)
10.9	--	Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan.
10.10	--	Form of Performance-Based Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.
10.11	--	Registrant's 2000 Employee Stock Purchase Plan.
10.12	--	Form of Employee Assignment of Patent Rights.(1)
10.13	--	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan.

10.14 -- Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 2000 Broad-Based Equity Incentive Stock Option Plan.

10.15 -- Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 2000 Broad-Based Equity Incentive Stock Option Plan entered into between the Registrant and its directors.

10.16 -- Severance Agreement dated January 11, 2000 entered into between Registrant and its executive officers, together with related schedule.

---

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

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

(3) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the year ended December 31, 1994 and incorporated herein by reference.

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

(5) 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.

(b) REPORTS ON FORM 8-K

On January 28, 2000, the Registrant filed the following report on Form 8-K:

Report dated January 14, 2000 which described the joint venture the Registrant entered into with Elan Corporation, plc. No financial statements were filed with this report on Form 8-K. Eight documents, including the Subscription, Joint Development and Operating Agreement, security and warrant purchase agreements and related license agreements (with certain confidential information deleted) were filed as exhibits to the report.

(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 27th day of March, 2000.

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 appoint 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)	March 27, 2000
/s/ B. LYNNE PARSHALL B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	March 27, 2000
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 27, 2000
/s/ ALAN C. MENDELSON Alan C. Mendelson	Director	March 27, 2000

SIGNATURES	TITLE	DATE
/s/ WILLIAM R. MILLER William R. Miller	Director	March 27, 2000
/s/ MARK B. SKALETSKY Mark B. Skaletsky	Director	March 27, 2000
/s/ LARRY SOLL Larry Soll	Director	March 27, 2000
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 27, 2000

INDEX TO EXHIBITS

EXHIBIT NUMBER		DESCRIPTION OF DOCUMENT
3.1	--	Amended and Restated Certificate of Incorporation.(1)
3.2	--	Bylaws.(1)
4.1	--	Reference is made to Exhibits 3.1, 3.2 and 10.19.
4.2	--	Ciba-Geigy Investor Rights Agreement between the Registrant and Novartis AG, formerly Ciba-Geigy Limited("Novartis"), dated November 9, 1990.(1)
4.3	--	Voting Rights Agreement among the Registrant, Novartis and Dr. Crooke, dated November 9, 1990.(1)
4.4	--	Specimen stock certificate.(1)
9.1	--	Reference is made to Exhibit 4.4.
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.(10)
10.3	--	Revised form of Incentive Stock Option Agreement under the 1989 Stock Option Plan.(8)
10.4	--	Revised form of Supplemental Stock Option Agreement under the 1989 Stock Option Plan.(8)
10.5	--	Form of Incentive Stock Option Agreement dated January 1, 1995 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.(4)
10.6	--	Form of Supplemental Stock Option Agreement dated January 1, 1995 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.(4)
10.7	--	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended.(8)
10.8	--	Revised form of Supplemental Stock Option Agreement under Registrant's 1992 Non-Employee Directors' Stock Option Plan.(9)
10.9	--	Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan.
10.10	--	Form of Performance-Based Supplemental Stock Option Agreement dated January 6, 2000 under the 1989 Stock Option Plan entered into between Registrant and certain of its officers together with related schedule.
10.11	--	Registrant's 2000 Employee Stock Purchase Plan.
10.12	--	Form of Employee Assignment of Patent Rights.(1)
10.13	--	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan.
10.14	--	Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 2000 Broad-Based Equity Incentive Stock Option Plan.
10.15	--	Form of Supplemental Stock Option Agreement dated January 6, 2000 under the 2000 Broad-Based Equity Incentive Stock Option Plan entered into between the Registrant and its directors.
10.16	--	Severance Agreement dated January 11, 2000 entered into between Registrant and its executive officers, together with related schedule.
10.17	--	Amended and Restated Research, Development and Licensing Agreement by and between Isis Pharmaceuticals, Inc. and Novartis AG dated February 13, 1996(with certain confidential information deleted).(7)
10.18	--	Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(5)
10.19	--	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(6)
10.20	--	Agreement between Registrant and CIBA Vision Corporation dated

July 10, 1997 (with certain confidential information deleted).(9)

EXHIBIT NUMBER		DESCRIPTION OF DOCUMENT
10.21	--	Amendment No. 2 to the Agreement between the Company and CIBA Vision Corporation, dated September 14, 1998 (with certain confidential information deleted).(12)
10.22	--	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.(9)
10.23	--	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.(9)
10.24	--	Purchase Agreement for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(10)
10.25	--	First Supplement to Purchase Agreement for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(11)
10.26	--	Asset Purchase Agreement between Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(10)
10.27	--	Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted).(11)
10.28	--	Research and Development Agreement between the Registrant and Zeneca Limited, dated December 18, 1998 (with certain confidential information deleted).(14)
10.29	--	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(13)
10.30	--	Subscription, Joint Development and Operating Agreement, dated April 20, 1999 by and among Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense, Ltd. (with certain confidential information deleted); together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreements and License Agreements.(16)
10.31	--	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and Isis Pharmaceuticals, Inc.; together with related Amendment to the Stock Purchase Agreement.(17)
10.32	--	Subscription, Joint Development and Operating Agreement, dated January 14, 2000 by and among 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.(18)
23.1	--	Consent of Ernst & Young LLP, Independent Auditors.
24.1	--	Power of Attorney. Reference is made to page 31.
27.1	--	Financial Data Schedule.
99.1	--	Form of Confidentiality Agreement.(15)

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(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 Registration Statement on Form S-8 (No. 33-42970) and incorporated herein by reference.

(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 1992 and incorporated herein by reference.

(4) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1994 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.

(6) 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.

(7) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1995 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, 1996 and incorporated herein by reference.

(9) 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.

(10) 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.

(11) 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.

(12) 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.

(13) 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.

(14) Filed as an exhibit to the Registrant's Annual Report on Form 10-K (Amendment No. 2) for the year ended December 31, 1998 and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto for the year ended December 31, 1998 and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.

(17) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.

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

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, 1999 and 1998, and the related statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 1999. 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, 1999 and 1998, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 1999, in conformity with accounting principles generally accepted in the United States.

ERNST & YOUNG LLP

San Diego, California
January 28, 2000,
except for paragraph 3
of Note 8, as to which
the date is March 8, 2000

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

	DECEMBER 31,	
	1999	1998
Current assets:		
Cash and cash equivalents	$ 35,296	$ 27,618
Short-term investments	17,543	31,230
Contracts receivable	5,429	3,466
Prepaids and other current assets	929	873
Total current assets	59,197	63,187
Property, plant and equipment, net	23,945	21,542
Patent costs, net	11,250	9,113
Investment in joint venture	6,991	--
Deposits and other assets	1,724	2,232
	$ 103,107	$ 96,074

LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)

Current liabilities:		
Accounts payable	$ 3,148	$ 2,977
Accrued payroll and related expenses	1,215	3,088
Accrued liabilities	2,563	2,714
Deferred contract revenues	4,166	10,176
Current portion of long-term obligations	3,892	3,581
Total current liabilities	14,984	22,536
Long-term obligations, less current portion	87,254	77,724
Commitments (See Note 3)		
Stockholders' equity (deficit):		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 15,000,000 shares authorized, 120,150 shares and no shares issued and outstanding at December 31, 1999 and 1998, respectively	12,315	--
Accretion of Preferred stock dividend	120	--
Common stock, $.001 par value; 50,000,000 shares authorized, 31,613,000 shares and 27,053,000 shares issued and outstanding at December 31, 1999 and 1998, respectively	32	27
Additional paid-in capital	245,192	192,737
Accumulated other comprehensive income (loss)	(29)	166
Accumulated deficit	(256,761)	(197,116)
Total stockholders' equity (deficit)	869	(4,186)
	$ 103,107	$ 96,074

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF OPERATIONS
(IN THOUSANDS, EXCEPT FOR PER SHARE AMOUNTS)

	YEAR ENDED DECEMBER 31,		
	1999	1998	1997
Revenues:			
Research and development revenues under collaborative agreements	$ 29,523	$ 38,611	$ 32,722
Research and development revenues from joint venture	4,402	--	--
Product revenues	--	560	--
	33,925	39,171	32,722
Expenses:			
Research and development	66,413	62,200	55,940
Write-off of acquired patents	--	5,238	--
General and administrative	10,571	9,511	8,078
Total operating expenses	76,984	76,949	64,018
Loss from operations	(43,059)	(37,778)	(31,296)
Equity in loss of joint venture	(7,242)	--	--
Interest income	2,500	4,150	3,815
Interest expense	(11,424)	(9,355)	(3,585)
Net loss	(59,225)	(42,983)	(31,066)
Accretion of dividend on preferred stock	(420)	--	--
Net loss applicable to common stock	$(59,645)	$(42,983)	$(31,066)
Basic and diluted net loss per share	$ (2.08)	$ (1.60)	$ (1.17)
Shares used in computing basic and diluted net loss per share	28,703	26,873	26,456

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
(IN THOUSANDS)

	PREFERRED STOCK			COMMON STOCK	
DESCRIPTION	SHARES	ACCRUED AMOUNT	DIVIDEND	SHARES	AMOUNT
Balance at December 31, 1996	--	$ --	$ --	26,201	$ 26
Comprehensive Income					
Net loss	--	--	--	--	--
Changes in unrealized gains and (losses), net of income taxes	--	--	--	--	--
Comprehensive income (loss)					
Options exercised and employee Stock purchase plan	--	--	--	454	1
Issuances of warrants to purchase Common stock				--	--
Compensation relating to the Granting of options	--	--	--	--	--
Balance at December 31, 1997	--	--	--	26,655	27
Comprehensive Income					
Net loss	--	--	--	--	--
Change in unrealized gains and (losses), net of income taxes	--	--	--	--	--
Comprehensive income (loss)					
Options exercised and employee Stock purchase plan	--	--	--	398	--
Issuances of warrants to purchase Common stock	--	--	--	--	--
Balance at December 31, 1998	--	--	--	27,053	27
Comprehensive Income					
Net loss	--	--	--	--	--
Change in unrealized gains and (losses), net of income taxes	--	--	--	--	--
Comprehensive income (loss)					
Issuance of preferred stock	120	12,015	--	--	--
Dividends accrued	--	--	420	--	--
Conversion of preferred stock dividends	--	300	(300)	--	--
Issuances of common stock, net of repurchases and offering costs	--	--	--	3,974	4
Warrants exercised	--	--	--	157	--
Options exercised and employee stock purchase plan	--	--	--	429	1
Compensation relating to the granting of options	--	--	--	--	--
Balance at December 31, 1999	120	$ 12,315	$ 120	31,613	$ 32

	PAID IN CAPITAL	ACCUMULATED OTHER COMPREHENSIVE INCOME/(LOSS)	ACCUMULATED DEFICIT	TOTAL STOCKHOLDERS' EQUITY
Balance at December 31, 1996	$ 181,248	$ 178	$(123,067)	$ 58,385
Comprehensive Income				
Net loss	--	--	(31,066)	(31,066)
Changes in unrealized gains and (losses), net of income taxes	--	(13)	--	(13)
Comprehensive income (loss)				(31,079)
Options exercised and employee Stock purchase plan	3,306	--	--	3,307
Issuances of warrants to purchase Common stock	3,780	--	--	3,780
Compensation relating to the Granting of options	459	--	--	459

Balance at December 31, 1997	188,793	165	(154,133)	34,852
Comprehensive Income				
Net loss	--	--	(42,983)	(42,983)
Change in unrealized gains and (losses), net of income taxes	--	1	--	1
Comprehensive income (loss)				(42,982)
Options exercised and employee Stock purchase plan	2,298	--	--	2,298
Issuances of warrants to purchase Common stock	1,646	--	--	1,646
Balance at December 31, 1998	192,737	166	(197,116)	(4,186)
Comprehensive Income				
Net loss	--	--	(59,645)	(59,645)
Change in unrealized gains and (losses), net of income taxes	--	(195)	--	(195)
Comprehensive income (loss)				(59,840)
Issuance of preferred stock	--	--	--	12,015
Dividends accrued	--	--	--	420
Conversion of preferred stock dividends	--	--	--	--
Issuances of common stock, net of repurchases and offering costs	49,051	--	--	49,055
Warrants exercised	17	--	--	17
Options exercised and employee stock purchase plan	3,250	--	--	3,251
Compensation relating to the granting of options	137	--	--	137
Balance at December 31, 1999	$ 245,192	$ (29)	$(256,761)	$ 869

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	YEAR ENDED DECEMBER 31,		
	1999	1998	1997
Operating activities:			
Net loss	$(59,225)	$(42,983)	$(31,066)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	5,196	4,258	3,178
Deferred interest on long term debt	8,077	6,112	654
Equity in losses of joint venture	7,242	--	--
Write-off of acquired patents	--	5,238	--
Compensation expense related to grant of options	137	--	459
Changes in operating assets and liabilities:			
Contracts receivable	(1,963)	(3,177)	(289)
Prepaids and other current assets	(56)	1,202	(343)
Accounts payable	171	134	481
Accrued payroll and related expenses	(1,873)	846	753
Accrued liabilities	(60)	(1,633)	1,584
Deferred contract revenues	(6,010)	(4,717)	4,689
Net cash used in operating activities	(48,364)	(34,720)	(19,900)
Investing activities:			
Short-term investments	13,492	17,455	(8,155)
Property, plant and equipment	(4,791)	(4,434)	(3,454)
Patent costs	(2,642)	(3,882)	(1,455)
Investment in joint venture	(14,233)	--	--
Deposits and other assets	276	(30)	(2,098)
Net cash provided by (used in) investing activities	(7,898)	9,109	(15,162)
Financing activities:			
Net proceeds from issuance of equity	64,338	3,944	7,087
Proceeds from long-term borrowing	3,233	13,354	32,666
Principal payments on debt and capital lease obligations	(3,631)	(2,171)	(3,671)
Net cash provided by financing activities	63,940	15,127	36,082
Net increase (decrease) in cash and cash equivalents	7,678	(10,484)	1,020
Cash and cash equivalents at beginning of year	27,618	38,102	37,082
Cash and cash equivalents at end of year	$ 35,296	$ 27,618	$ 38,102
Supplemental disclosures of cash flow information:			
Interest paid	$ 2,402	$ 3,191	$ 2,644
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt and capital lease obligations for acquisitions of property, plant and equipment	$ 2,071	$ 2,068	$ 2,953
Additions to debt for patent acquisitions	$ --	$ 3,238	$ --
Conversion of preferred stock dividends into preferred stock	$ 300	$ --	$ --

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1999

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 was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc., in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share--Basic earnings per share is based on weighted average common shares outstanding and excludes any dilutive effects of options, warrants and convertible securities. Dilutive earnings per share includes the dilutive effects of options, warrants and convertible securities. 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, 1999, 1998 and 1997, costs and expenses of approximately $26,000,000, $35,000,000 and $31,000,000, 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 these fees is recorded when no further performance obligations exist in accordance with Staff Accounting Bulletin No. 101.

Cash equivalents and short-term investments--Cash equivalents and short-term investments consist of highly liquid debt instruments. Isis considers instruments with original maturities of less than 90 days to be cash equivalents. Isis has recorded its cash equivalents and short-term investments at fair market value as of December 31, 1999, and has classified all of its investments as available-for-sale. Unrealized gains and losses, net of the related tax effect, are included in accumulated other comprehensive income (loss), a separate component of stockholders' equity (deficit). 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,	
	1999	1998
Land	$ 1,163	$ 1,163
Buildings and improvements	16,911	16,084
Equipment	31,075	25,324
Furniture and fixtures	1,510	1,227
	50,659	43,798
Less accumulated depreciation	(26,714)	(22,256)
	$ 23,945	$ 21,542

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: Intangible Assets and are adjusted to an appropriate amortization period, which results in an immediate write-off. Accumulated patent costs are amortized on a straight-line basis 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, 1999 and 8.2 years for December 31, 1998. Accumulated amortization was $999,000 at December 31, 1999 and $493,000 at December 31, 1998.

Investment in joint venture--On April 20, 1999, Isis and Elan Corporation, plc formed a joint venture to develop technology for the formulation of oral oligonucleotide drugs. The joint venture, Orasense, Ltd., a Bermuda limited company, is initially owned 80.1% by Isis and 19.9% by Elan. While Isis owns 80.1% of the outstanding common stock of Orasense, 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 Orasense under the equity method of accounting.

Long-lived assets-- Long-lived assets are reviewed for potential impairment annually or when events and circumstances warrant an earlier review. When an evaluation is required, we compare the estimated future undiscounted cash flows associated with the asset to the asset's carrying amount to determine if a write-down to fair market value is required.

Use of estimates--The preparation of financial statements in conformity with generally accepted accounting principles 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 (FAS) 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, FAS 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, 1999, 1998 and 1997 have been reflected in the Consolidated Statement of Stockholders' Equity (Deficit).

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

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 losses on its short-term investments. As of December 31, 1999, 75% of the debt securities held by Isis had a contractual maturity of one year or less, and the remaining 25% of the portfolio was due within 2.5 years.

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

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS (LOSSES)	ESTIMATED FAIR VALUE
DECEMBER 31, 1999		(in thousands)	
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
DECEMBER 31, 1998			
U.S. Treasury securities and obligations of U.S. Government agencies	$20,700	$ 86	$20,786
U.S. corporate debt securities	10,364	80	10,444
Total debt securities	$31,064	$ 166	$31,230

3. LONG-TERM OBLIGATIONS AND COMMITMENTS

Between 1997 and 1998, Isis obtained a total of $40,060,000 in private debt financing. The terms of the financing provide for a 10 year maturity on the debt, interest of 14% per annum and deferred interest payments for the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan, November 1, 2007. No principal repayments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $78 million on November 1, 2002. In conjunction with the debt financing, Isis issued warrants to the lender to purchase shares of common stock, exercisable at $25 per share. Isis issued warrants for a total of 800,000 common shares. 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 and expected volatility of 60 percent. The assumed risk free interest rate was 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 is carried on the balance sheet net of the unamortized amount allocated to the warrants, and including accrued interest. The carrying amount at December 31, 1999 was $49,086,000. The fair value of this debt at December 31, 1999 approximated $52,000,000. 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 1997, Isis obtained 2 new 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 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 the note at December 31, 1999 was $3,290,000. 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, 1999 was $4,500,000. As of December 31, 1999, the carrying value of these variable rate long-term notes approximated fair value.

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 7 year U.S. interbanking rate plus 2.0%, determined at the time each advance was made. Interest payments are due twice each year with principal repayment due 7 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, 1999 was $22,576,000, which approximated fair value.

In December 1998, Isis purchased from Gilead Sciences, Inc., the holdings of its antisense patent estate. This acquisition includes 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. The first payment for $2,000,000 was paid in December 1998 and an additional $1,000,000 was paid in December 1999. Isis has recorded the net present value of the future

payments, using a discount rate of 10%, as a long-term obligation on the balance sheet. The balance of this obligation at December 31, 1999 was $2,568,000, which approximated fair value.

Between September and November 1999, Isis borrowed a total of $2,213,000 under a $18,400,000 debt facility made available under the terms of its joint venture with Elan Corporation, plc. The borrowed funds were used to fund research and development costs associated with the joint venture. The terms of the financing provide for a 6 year maturity on the debt, with interest at 12% per annum, compounded semi-annually. No principal or interest payments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $4.2 million on April 19, 2005. 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 the average market value over the 60 trading days ending two business days prior to the maturity date. The balance under this borrowing facility as of December 31, 1999 was $2,284,000, which approximated fair value.

In September 1999, Isis borrowed $1,019,000 from Abbott Laboratories 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 2 year maturity on the debt, with an annual interest rate of 2% over the Citibank prime rate calculated at the date of borrowing and reset annually. Interest is payable annually. The principal, which is due at maturity, can be paid in cash, 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, 1999 was $1,019,000, which approximated fair value.

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through February 2007. Annual future minimum payments under operating leases and other long-term obligations as of December 31, 1999 are as follows (in thousands):

	OPERATING LEASES	CAPITAL LEASES	CONTRACT OBLIGATIONS	LONG-TERM DEBT
2000	$ 1,930	$ 2,638	$ 1,000	$ 3,427
2001	2,023	2,226	2,000	3,364
2002	1,824	1,191		9,611
2003	1,772	516		28,955
2004	1,594			17,592
Thereafter	6,070			148,981
Total minimum payments	$ 15,213	$ 6,571	$ 3,000	211,930
Less amount representing interest		(750)	(432)	(129,173)
Present value of future minimum payments		5,821	2,568	82,757
Less current portion		(2,230)	(913)	(749)
Total		$ 3,591	$ 1,655	$ 82,008

Rent expense for the years ended December 31, 1999, 1998, and 1997 was $1,736,000, $1,760,000 and $1,431,000, respectively. Cost of equipment under capital leases at December 31, 1999 and 1998 was $8,394,000 and $7,101,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 1999 and 1998 was $4,633,000 and $3,140,000, respectively.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS - (CONTINUED)
DECEMBER 31, 1999

4. STOCKHOLDERS' EQUITY

Stock Option Plans and Other Employee Option Grants--In June 1989, Isis adopted a stock option plan which provides for the issuance of incentive and non-qualified stock options for the purchase of up to 10,200,000 shares of common stock to its employees and certain other individuals. In addition to the options issued under the terms of the 1989 plan, non-qualified options to purchase 319,000 shares of common stock have been granted to certain employees. 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 4 year period, with 25% exercisable at the end of 1 year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vest over a 5 year period. At December 31, 1999, a total of 5,127,000 shares were exercisable, and 945,000 were available for future grant.

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 its non-employee directors. Options under this plan expire 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in 4 equal annual installments beginning 1 year after the date of grant. Options granted before January 1, 1996 vest over a 5 year period. At December 31, 1999, 163,000 shares issued under this plan were exercisable and 60,000 Shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 1997 through December 31, 1999 (in thousands, except per share data):

	NUMBER OF SHARES	PRICE PER SHARE	WEIGHTED AVG PRICE/SHARE
Outstanding at December 31, 1996	6,093	$ .14 to $20.00	$ 8.48
Granted	1,071	13.19 to 19.88	
Exercised	(395)	.14 to 16.00	
Terminated	(327)	3.75 to 18.25	
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

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 12/31/99	WEIGHTED AVERAGE REMAINING CONTRACTUAL LIFE	WEIGHTED AVERAGE EXERCISE PRICE	NUMBER EXERCISABLE AS OF 12/31/99	WEIGHTED AVERAGE EXERCISE PRICE
-					

during 1997, 1998 and 1999. The weighted average risk free interest rates for 1997, 1998 and 1999 were 5.7%, 4.6%, and 6.2%, respectively. All options granted during the year were valued using the same risk-free rate for the year. The weighted average fair value of options granted was $8.50 for 1997, $5.98 for 1998 and $6.41 for 1999.

Warrants -- In 1997 and 1998, Isis issued 500,000 and 300,000 warrants, respectively, in conjunction with a private debt financing agreement. As of December 31, 1999, 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. As of December 31, 1999, all of the warrants remain outstanding at an exercise price of $24 per share. The warrants expire April 19, 2004.

As of December 31, 1999, total common shares reserved for future issuance was 9,722,000.

5. INCOME TAXES

Significant components of Isis' deferred tax assets as of December 31, 1999 and 1998 are shown below. Valuation allowances of $113,814,000 and $90,931,000 have been recognized for 1999 and 1998, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	1999	1998
Deferred tax assets:		
Capitalized research expense	$ 9,800,000	$ 8,320,000
Net operating loss carryforwards	87,990,000	69,661,000
Research and development credits	13,910,000	10,849,000
Other, net	6,404,000	5,314,000
Total deferred tax assets	118,104,000	94,144,000
Deferred tax liabilities:		
Patent expense	(4,290,000)	(3,213,000)
Total deferred tax liabilities	(4,290,000)	(3,213,000)
Total net deferred tax assets	113,814,000	90,931,000
Valuation allowance for deferred tax assets	(113,814,000)	(90,931,000)
Net deferred tax assets	$ 0	$ 0

At December 31, 1999, approximately $5,114,000 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, 1999, Isis had federal and California tax net operating loss carryforwards of approximately $245,904,000 and $33,451,000, respectively. Isis also had federal and California research credit carryforwards of approximately $10,678,000 and $4,970,000, 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 $198,000 of the California tax loss carryforward expired during 1999 and the related deferred tax asset and tax loss carryforward amounts have been reduced accordingly. The remaining California tax loss carryforward will begin expiring in 2000, 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 the companies' 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. Included in the statement of operations for the years ended December 31, 1999, 1998 and 1997 are contract revenues arising from this collaboration totaling $7,527,000, $15,641,000 and $21,106,000, respectively.

In July 1997, Isis and CIBA Vision Corporation entered into an agreement granting CIBA Vision exclusive worldwide distribution rights for Vitravene(TM) (fomivirsen). Under the terms of the agreement, Isis will manufacture and sell Vitravene(TM) to CIBA Vision at a price that will allow Isis and CIBA Vision to share the commercial value of the product. CIBA Vision will market and sell Vitravene(TM) worldwide and will be responsible for regulatory approvals outside of the United States and Europe. Additionally, CIBA Vision received the option to acquire the exclusive license to market and distribute a second generation antisense compound to treat CMV retinitis (ISIS 13312) which Isis is currently developing. At the inception of the agreement, CIBA Vision paid us a $5 million non-refundable pre-commercial fee to partially reimburse Isis for the costs incurred in discovering and developing Vitravene(TM) to that point. That payment was recognized as revenue in 1997 and included in the statement of operations as contract revenue. In August 1998, the FDA approved Vitravene(TM) for marketing, and in the fourth quarter of the year CIBA Vision began selling Vitravene(TM) commercially. Isis delivered its first commercial shipment of Vitravene(TM) to CIBA Vision in the third quarter of 1998 and recorded $560,000 in net product revenues. Isis did not recognize any revenue during 1999 for sales of Vitravene(TM) but expects to recognize modest revenues early in 2000. Under the CIBA Vision agreement, Isis received a $2,500,000 milestone payment in 1999 and earned contract revenue of $7,500,000 in 1998 and $5,000,000 (which represents the pre-commercial fee described above) in 1997.

In July 1995, Isis and Boehringer Ingelheim International GmbH signed definitive agreements and completed the formation of a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28,500,000 in cash plus certain license rights. Of the $28,500,000, $21,300,000 was accounted for as equity and $7,200,000 was accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and

development costs under the collaboration. In December 1996, coinciding with the achievement of a milestone, Boehringer Ingelheim purchased 409,000 shares of common stock for $10,000,000. Of that total, $6,000,000 was accounted for as equity and $4,000,000 as deferred revenue. In September 1999 we announced that we had reacquired full rights to ISIS 2302 from Boehringer Ingelheim. Boehringer Ingelheim and Isis provided equal funding for the combined research and development program. Boehringer Ingelheim had also provided Isis with a line of credit to be used in support of the combined programs. As of December 31, 1999, the outstanding balance under this line of credit was $22,576,000. Since we have reacquired the rights to ISIS 2302, there will be no further draws against this line. The statement of operations for the years ended December 31, 1999, 1998 and 1997 reflects contract revenues of $6,974,000, $6,544,000 and $5,603,000, respectively, from this collaboration.

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 our antisense program. The three year collaboration provides us 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, 1999 and 1998, reflects contract revenues of $3,500,000 and $3,875,000, respectively, from Merck under the terms of this agreement.

In August 1998, Isis granted an exclusive license to our patents covering immune stimulation by phosphorothioate oligonucleotides to CpG ImmunoPharmaceuticals, Inc. The agreement grants exclusive worldwide rights to the methods and applications covered by issued U.S. Patents No. 5,663,153; No. 5,723,335; and related patent applications, not including claims for antisense therapeutics. Under the terms of the agreement, Isis received $5 million in 1998 and a 5% equity position in CpG ImmunoPharmaceuticals, Inc. Isis will also receive a portion of any sublicensing revenue relating to the technology. In 1998, Isis recorded revenue for the $5 million licensing fee, as there are no further performance obligations. Isis did not record revenue for the value of the 5% equity position, since realization of this asset is uncertain.

In November 1998, Isis sublicensed to Pantheco A/S, a Danish biotechnology company, our Peptide Nucleic Acid technology for the creation of anti-infective drugs. As the exclusive licensee, Isis will retain the rights for all other areas of human therapeutics. As part of this transaction, Isis received a 24.9% equity position in Pantheco A/S. Isis did not record any revenue related to this transaction, since realization of the value of the equity interest in Pantheco is uncertain.

In December 1998, Isis purchased from Gilead Sciences, Inc. the holdings of its antisense patent estate. This acquisition includes 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 and a second payment of $1,000,000 in December 1999. 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, 1999 and December 31, 1998 was $2,568,000 and $3,238,000, 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 developed into potentially viable products. The scope of the effort to be invested by Isis' scientists is within the bounds of its existing research and development budgets. Because Isis scientists are just beginning to work with the Gilead patents and there is no assurance that research and development efforts related to these patents will be successful, Isis wrote off the acquired patents in 1998.

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 from AstraZeneca at least $7 million for a technology access fee and annual research funding during the first two years of the collaboration. Isis estimates that it may potentially receive more than $40 million from this collaboration, including a technology access fee, annual research funding, and milestone payments for drugs progressing into clinical development. Isis will receive royalties on the sales of any marketed drug arising out of the collaboration. The initial term of the research collaboration is three years. In December 1998, AstraZeneca paid $2,000,000 in technology access fees which was accounted for as deferred revenue. The statement of operations for the year ended December 31, 1999 reflects contract revenues of $3,420,000 from AstraZeneca under the terms of this agreement.

Also in December 1998, Isis entered into a 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 upfront 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 initial term of the research collaboration is two years. In December 1998, Isis received an initial payment of $250,000 which was accounted for as deferred revenue. The statement of operations for the year ended December 31, 1999 reflects contract revenues of $1,250,000 from Abbott under the terms of this agreement.

In April 1999, Isis and Elan Corporation, plc 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 April 1999, Isis contributed $12,015,000 to Orasense as the purchase price for 9,612 shares of Orasense common stock. During the year, Elan purchased convertible debt from Isis in the amount of $2,213,000, which Isis used to provide additional development funding to Orasense. For the year ended December 31, 1999, Isis recorded $4,402,000 in revenue from Orasense, and recorded $7,242,000 as equity in the net loss of Orasense.

In September 1999, Isis entered into a collaboration with Aventis S.A. (formerly Rhone-Poulenc Rorer) under which Isis will use its prorietary Antisense Target Validation technology to assess genes identified within Aventis' genomics programs. This collaboration will enable Aventis to determine the function and therapeutic value of numerous novel gene targets and use this information about gene function to develop pharmaceutical products. It also will provide Isis with valuable information on these targets to assist in the development of novel antisense drugs. The agreement specifies that Isis will receive from Aventis a commitment fee, as well as success and proof of concept fees, based on Isis demonstrating target inhibition as specified in the contract. Isis will be entitled to certain milestone payments based on milestones achieved by Aventis. Isis will also be obligated to pay certain milestone payments based on milestones achieved by Isis. In addition, Isis will be required to pay Aventis royalty payments based on net sales of any Isis royalty bearing

products. In 1999, Isis received $613,000 in commitment and proof of concept fees from Aventis. The statement of operations for the year ended December 31, 1999 reflects contract revenues of $200,000 from Aventis under the terms of this agreement, with the balance recorded on the balance sheet as deferred revenue.

7. JOINT VENTURE SUPPLEMENTARY DISCLOSURE

Due to the significant minority investor rights retained by Elan Corporation, plc 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 December 31, 1999.

	1999
BALANCE SHEET:	
Assets	
Cash and cash equivalents	$ 6
In-license costs, net	11,250
Total assets	$ 11,256
Liabilities and Stockholders' Equity	
Amounts due to affiliates	$ 2,534
Common stock, $1.00 par value; 12,000 shares authorized, 12,000 shares outstanding at December 31, 1999	12
Additional paid-in capital	17,751
Accumulated deficit	(9,041)
Total liabilities and stockholders' equity	$ 11,256
RESULTS OF OPERATIONS:	
Revenues	$ --
Research and development expenses	9,041
Net loss	$ (9,041)

8. SUBSEQUENT EVENTS

In December 1999, the unexpected failure of our pivotal clinical trial of ISIS 2302 in Crohn's disease prompted the restructuring of the company. In January 2000, we announced a restructuring plan to reduce expenses and focus resources on the development of antisense drugs with significant commercial potential. In conjunction with this restructuring, we will reduce Isis' workforce by approximately 140 employees in the first four months of 2000. We estimate that costs associated with this restructuring will approximate $2 million which will be recorded in the first quarter of 2000.

In January 2000, Isis and Elan Corporation agreed to form a new subsidiary of Isis to develop an antisense drug, ISIS 14803, to treat patients chronically infected with Hepatitis C virus (HCV). The new subsidiary is called HepaSense and plans to develop and commercialize this novel therapeutic for HCV while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD(R) Drug Delivery System, a disposable subcutaneous infusion device. ISIS 14803 began Phase I clinical trials in early 2000. Isis and Elan have each licensed technology to HepaSense. As part of the transaction, Elan will purchase $7.5 million of Isis common stock in April 2000 and potentially an additional $7.5 million of common stock upon completion of a mutually agreed milestone. Both tranches will be purchased at a premium to Isis' market price. Elan will also purchase Isis Series B Preferred Stock which will be convertible in the future into either Isis common stock or stock in HepaSense. In addition, Elan will make available to Isis a $12.0 million line of credit for Isis' funding commitment to HepaSense.

On March 8, 2000, we sold 1,000,000 shares of our common stock to an institutional investor at a negotiated price of $27.25 per share. In addition, during the first quarter of 2000 we sold 1,551,614 shares of our common stock to Ridgeway Investment Limited at an average purchase price of $9.67 per share under the terms of the Common Stock Purchase Agreement filed as an exhibit to the prospectus dated December 6, 1999. The $9.67 per share average purchase price reflects the average trading prices of the common stock on the Nasdaq National Market during the respective drawdown periods. We did not pay any other compensation in conjunction with these sales of our common stock.

EXHIBIT 10.9

Optionee: _____ Date: _____

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:_____

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting)(1)
_____	_____
_____	_____

Exercise Price Per Share: (2) _____ Expiration Date: _____ (3)

Percentage of Full-Time Work: 100%

Isis Pharmaceuticals, Inc.

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

Optionee: _____
Address:

OPTIONEE:

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 acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) The option will vest monthly with 4.167% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, a reduced number of shares will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. Increases of work percentage up to but not in excess of the Percentage of Full Time Work specified above will result in a corresponding increase in the percentage of shares vesting. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

(2) Not less than 85% of the fair market value of the Common Stock on the date of grant of this option.

(3) Less than 10 years from the date of grant of this option.

EXHIBIT 10.10

Optionee: _____ Date: _____

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:_____

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting)(1)
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*THIS OPTION WILL NOT BE EXERCISABLE, INCLUDING ANY VESTED SHARES, UNTIL 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 PRESENTED TO THE BOARD OF DIRECTORS ON JANUARY 6, 2000, IS SUCCESSFUL; AND (4) THE COMPANY HAS COMPLETED AT LEAST ONE NEW CORPORATE PARTNERSHIP. IF SUCH OBJECTIVES ARE NOT MET BY JANUARY 6, 2002 OR WAIVED BY THE BOARD OF DIRECTORS, THIS OPTION WILL TERMINATE.

Exercise Price Per Share: << >>(2) Expiration Date:<< >>(3)

Isis Pharmaceuticals, Inc.

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

Optionee: _____
Address:

OPTIONEE:

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 acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) After the first year, the option will vest monthly with 2.08% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, a reduced number of shares will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. Increases of work percentage up to but not in excess of the Percentage of Full Time Work specified above will result in a corresponding increase in the percentage of shares vesting. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

(2) Not less than 85% of the fair market value of the Common Stock on the date of grant of this option.

(3) Less than 10 years from the date of grant of this option.

ISIS PHARMACEUTICALS, INC.
SUPPLEMENTAL STOCK OPTION AGREEMENT

SCHEDULE

NAME OF OPTIONEE	NUMBER OF SHARES
Stanley T. Crooke	250,000
B. Lynne Parshall	170,000
Debby Jo Blank	100,000

EXHIBIT 10.11

ISIS PHARMACEUTICALS, INC.

2000 EMPLOYEE STOCK PURCHASE PLAN

APPROVED BY THE BOARD OF DIRECTORS JANUARY 6, 2000
APPROVED BY STOCKHOLDERS JUNE 8, 2000

1. PURPOSE.

(a) The purpose of this 2000 Employee Stock Purchase Plan (the "Plan") is to provide a means by which employees of Isis Pharmaceuticals, Inc. (the "Company") and its Affiliates, as defined in Subsection 1(b), which are designated as provided in Subsection 2(b), may be given an opportunity to purchase common stock of the Company (the "Common Stock"). This Plan supersedes and replaces the Employee Stock Purchase Plan adopted by the Company on September 5, 1991.

(b) The word "Affiliate" as used in the Plan means any parent corporation or subsidiary corporation of the Company, as those terms are defined in Sections 424(e) and (f), respectively, of the Internal Revenue Code of 1986, as amended (the "Code").

(c) The Company, by means of the Plan, seeks to retain the services of its employees, to secure and retain the services of new employees, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the rights to purchase stock of the Company granted under the Plan be considered options issued under an "employee stock purchase plan" as that term is defined in Section 423(b) of the Code.

2. ADMINISTRATION.

(a) The Plan shall be administered by the Board of Directors (the "Board") of the Company unless and until the Board delegates administration to a Committee, as provided in Subsection 2(c). Whether or not the Board has delegated administration, the Board shall have the final power to determine all questions of policy and expediency that may arise in the administration of the Plan.

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

(i) To determine when and how rights to purchase stock of the Company shall be granted and the provisions of each offering of such rights (which need not be identical).

(ii) To designate from time to time which Affiliates of the Company shall be eligible to participate in the Plan.

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

(iv) To amend the Plan as provided in Section 13.

(v) To terminate or suspend the Plan as provided in Section 15.

(vi) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and its Affiliates and to carry out the intent that the Plan be treated as an "employee stock purchase plan" within the meaning of Section 423 of the Code.

(c) The Board may delegate administration of the Plan to a Committee composed of not fewer than two (2) members of the Board (the "Committee"). If administration is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish the Committee at any time and revest in the Board the administration of the Plan.

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of Section 12 relating to adjustments upon changes in stock, the stock that may be sold pursuant to rights granted under the Plan shall not exceed in the aggregate two hundred thousand (200,000) shares of Common Stock (the "Reserved Shares"). As of the first nine (9) anniversaries of the Effective Date of the Plan, the number of Reserved Shares will be increased automatically by the lesser of (i) one percent (1%) of the total number of shares of Common Stock outstanding on such anniversary date or (ii) two hundred thousand (200,000) shares. If any right granted under the Plan shall for any reason terminate without having been exercised, the Common Stock not purchased under such right shall again become available for the Plan.

(b) The stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

4. GRANT OF RIGHTS; OFFERING.

The Board or the Committee may from time to time grant or provide for the grant of rights to purchase Common Stock of the Company under the Plan to eligible employees (an "Offering") on a date or dates (the "Offering Date(s)") selected by the Board or the Committee. Each Offering shall be in such form and shall contain such terms and conditions as the Board or the Committee shall deem appropriate, which shall comply with the requirements of Section

423(b)(5) of the Code that all employees granted rights to purchase stock under the Plan shall have the same rights and privileges. The terms and conditions of an Offering shall be incorporated by reference into the Plan and treated as part of the Plan. The provisions of separate Offerings need not be identical, but each Offering shall include (through incorporation of the provisions of this Plan by reference in the document comprising the Offering or otherwise) the period during which the Offering shall be effective, which period shall not exceed twenty-seven (27) months beginning with the Offering Date, and the substance of the provisions contained in Sections 5 through 8, inclusive.

5. ELIGIBILITY.

(a) Rights may be granted only to employees of the Company or, as the Board or the Committee may designate as provided in Subsection 2(c), to employees of any Affiliate of the Company. Except as provided in Subsection 5(b), an employee of the Company or any Affiliate shall not be eligible to be granted rights under the Plan unless, on the Offering Date, such employee has been in the employ of the Company or any Affiliate for such continuous period preceding such grant as the Board or the Committee may require, but in no event shall the required period of continuous employment be greater than two (2) years. In addition, unless otherwise determined by the Board or the Committee and set forth in the terms of the applicable Offering, no employee of the Company or any Affiliate shall be eligible to be granted rights under the Plan, unless, on the Offering Date, such employee's customary employment with the Company or such Affiliate is for at least twenty (20) hours per week and at least five (5) months per calendar year. The Company, in its sole discretion, may exclude from participation in the Plan employees of the Company or any Affiliate of the Company who reside and/or perform services in certain specific jurisdictions if the laws of those jurisdictions make participation in the Plan impractical.

(b) The Board or the Committee may provide that each person who, during the course of an Offering, first becomes an eligible employee of the Company or designated Affiliate will, on a date or dates specified in the Offering which coincides with the day on which such person becomes an eligible employee or occurs thereafter, receive a right under that Offering, which right shall thereafter be deemed to be a part of that Offering. Such right shall have the same characteristics as any rights originally granted under that Offering, as described herein, except that:

(i) the date on which such right is granted shall be the "Offering Date" of such right for all purposes, including determination of the exercise price of such right;

(ii) the period of the Offering with respect to such right shall begin on its Offering Date and end coincident with the end of such Offering; and

(iii) the Board or the Committee may provide that if such person first becomes an eligible employee within a specified period of time before the end of the Offering, he or she will not receive any right under that Offering.

(c) No employee shall be eligible for the grant of any rights under the Plan if, immediately after any such rights are granted, such employee owns stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or of any Affiliate. For purposes of this Subsection 5(c), the rules of Section 424(d) of the Code shall apply in determining the stock ownership of any employee, and stock which such employee may purchase under all outstanding rights and options shall be treated as stock owned by such employee.

(d) An eligible employee may be granted rights under the Plan only if such rights, together with any other rights granted under "employee stock purchase plans" of the Company and any Affiliates, as specified by Section 423(b)(8) of the Code, do not permit such employee's rights to purchase stock of the Company or any Affiliate to accrue at a rate which exceeds twenty-five thousand dollars ($25,000) of fair market value of such stock (determined at the time such rights are granted) for each calendar year in which such rights are outstanding at any time.

(e) Officers of the Company and any designated Affiliate shall be eligible to participate in Offerings under the Plan; provided, however, that the Board may provide in an Offering that certain employees who are highly compensated employees within the meaning of Section 423(b)(4)(D) of the Code shall not be eligible to participate.

6. RIGHTS; PURCHASE PRICE.

(a) On each Offering Date, each eligible employee, pursuant to an Offering made under the Plan, shall be granted the right to purchase up to the number of shares of Common Stock of the Company purchasable with a percentage designated by the Board or the Committee not exceeding ten percent (10%) of such employee's Earnings (as defined in Subsection 7(a)) during the period which begins on the Offering Date (or such later date as the Board or the Committee determines for a particular Offering) and ends on the date stated in the Offering, which date shall be no later than the end of the Offering. In addition, the Board or the Committee may specify a maximum dollar amount that each employee may use to purchase shares during any Offering made under the Plan. The Board or the Committee shall establish one or more dates during an Offering (the "Exercise Date(s)") on which rights granted under the Plan shall be exercised and purchases of Common Stock carried out in accordance with such Offering.

(b) In connection with each Offering made under the Plan, the Board or the Committee may specify a maximum number of shares that may be purchased by any employee as well as a maximum aggregate number of shares that may be purchased by all eligible employees pursuant to such Offering. In addition, in connection with each Offering that contains more than one Exercise Date, the Board or the Committee may specify a maximum aggregate number of shares which may be purchased by all eligible employees on any given Exercise Date under the Offering. If the aggregate purchase of shares upon exercise of rights granted under the Offering would exceed any such maximum aggregate number, the Board or the Committee shall make a pro rata allocation of the shares available in as nearly a uniform manner as shall be practicable and as it shall deem to be equitable.

(c) The purchase price of stock acquired pursuant to rights granted under the Plan shall be not less than the lesser of:

(i) an amount equal to eighty-five percent (85%) of the fair market value of the stock on the Offering Date; or

(ii) an amount equal to eighty-five percent (85%) of the fair market value of the stock on the Exercise Date.

7. PARTICIPATION; WITHDRAWAL; TERMINATION.

(a) An eligible employee may become a participant in the Plan pursuant to an Offering by delivering a participation agreement to the Company within the time specified in the Offering, in such form as the Company provides. Each such agreement shall authorize payroll deductions of up to the maximum percentage specified by the Board or the Committee of such employee's Earnings during the Offering. "Earnings" is defined as the total compensation paid to an employee including all salary, wages (including amounts thereof elected to be deferred by the employee, that would otherwise have been paid, under any arrangement established by the Company that is intended to comply with Section 125, Section 401(k), Section 402(h) or Section 403(b) of the Code or that provides non-qualified deferred compensation), which shall include overtime pay, commissions, bonuses and other remuneration paid directly to the employee, but shall exclude profit sharing, the cost of employee benefits paid for by the Company or an Affiliate, education or tuition reimbursements, imputed income arising under any group insurance or benefit program, traveling expenses, business and moving expense reimbursements, income received in connection with stock options, contributions made by the Company or an Affiliate under any employee benefit plan, and similar items of compensation, as determined by the Board or the Committee. The payroll deductions made for each participant shall be credited to an account for such participant under the Plan and shall be deposited with the general funds of the Company. A participant may reduce (including to zero) or increase such payroll deductions, and an eligible employee may begin such payroll deductions, after the beginning of any Offering only as provided for in the Offering. A participant may make additional payments into his or her account only if specifically provided for in the Offering and only if the participant has not had the maximum permitted amount withheld during the Offering.

(b) At any time during an Offering, a participant may terminate his or her payroll deductions under the Plan and withdraw from the Offering by delivering to the Company a notice of withdrawal in such form as the Company provides. Such withdrawal may be elected at any time prior to the end of the Offering except as provided by the Board or the Committee in the Offering. Upon such withdrawal from the Offering by a participant, the Company shall distribute to such participant all of his or her accumulated payroll deductions (reduced to the extent, if any, such deductions have been used to acquire stock for the participant) under the Offering, without interest, and such participant's interest in that Offering shall be automatically terminated. A participant's withdrawal from an Offering will have no effect upon such participant's eligibility to re-enroll in the Offering or to participate in any other Offerings under the Plan but such participant will be required to deliver a new participation agreement in order to participate in subsequent Offerings under the Plan.

(c) Rights granted pursuant to any Offering under the Plan shall terminate immediately upon cessation of any participating employee's employment with the Company and any designated Affiliate, for any reason, and the Company shall distribute to such terminated employee all of his or her accumulated payroll deductions (reduced to the extent, if any, such deductions have been used to acquire stock for the terminated employee), under the Offering, without interest.

(d) Rights granted under the Plan shall not be transferable by a participant otherwise than by will or the laws of descent and distribution, or by a beneficiary designation as provided in Section 14 and, otherwise during his or her lifetime, shall be exercisable only by the person to whom such rights are granted.

8. EXERCISE.

(a) On each Exercise Date specified therefor in the relevant Offering, each participant's accumulated payroll deductions and other additional payments specifically provided for in the Offering (without any increase for interest) will be applied to the purchase of whole shares of stock of the Company, up to the maximum number of shares permitted pursuant to the terms of the Plan and the applicable Offering, at the purchase price specified in the Offering. No fractional shares shall be issued upon the exercise of rights granted under the Plan. The amount, if any, of accumulated payroll deductions remaining in each participant's account after the purchase of shares which is less than the amount required to purchase one share of stock on the final Exercise Date of an Offering shall be held in each such participant's account for the purchase of shares under the next Offering under the Plan, unless such participant withdraws from such next Offering, as provided in Subsection 7(b), or is no longer eligible to be granted rights under the Plan, as provided in Section 5, in which case such amount shall be distributed to the participant after such final Exercise Date, without interest. The amount, if any, of accumulated payroll deductions remaining in any participant's account after the purchase of shares which is equal to the amount required to purchase whole shares of stock on the final Exercise Date of an Offering shall be distributed in full to the participant after such Exercise Date, without interest.

(b) No rights granted under the Plan may be exercised to any extent unless the shares to be issued upon such exercise under the Plan (including rights granted thereunder) are covered by an effective registration statement pursuant to the Securities Act of 1933, as amended (the "Securities Act") and the Plan is in material compliance with all applicable state, foreign and other securities and other laws applicable to the Plan. If on an Exercise Date in any Offering hereunder the Plan is not so registered or in such compliance, no rights granted under the Plan or any Offering shall be exercised on such Exercise Date, and the Exercise Date shall be delayed until the Plan is subject to such an effective registration statement and such compliance, except that the Exercise Date shall not be delayed more than twelve (12) months and the Exercise Date shall in no event be more than twenty-seven (27) months from the Offering Date. If on the Exercise Date of any Offering hereunder, as delayed to the maximum extent permissible, the Plan is not registered and in such compliance, no rights granted under the Plan or any Offering shall be exercised and all payroll deductions accumulated during the Offering (reduced to the extent, if

any, such deductions have been used to acquire stock) shall be distributed to the participants, without interest.

9. COVENANTS OF THE COMPANY.

(a) During the terms of the rights granted under the Plan, the Company shall keep available at all times the number of shares of stock required to satisfy such rights.

(b) The Company shall seek to obtain from each federal, state, foreign or other regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock upon exercise of the rights granted under the Plan. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell stock upon exercise of such rights unless and until such authority is obtained.

10. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to rights granted under the Plan shall constitute general funds of the Company.

11. RIGHTS AS A STOCKHOLDER.

A participant shall not be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to rights granted under the Plan unless and until the participant's shareholdings acquired upon exercise of rights under the Plan are recorded in the books of the Company.

12. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) If any change is made in the stock subject to the Plan, or subject to any rights granted under the Plan, due to a change in corporate capitalization and without the receipt of consideration by the Company (through reincorporation, stock dividend, stock split, reverse stock split, combination or reclassification of shares), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the Plan pursuant to subsection 3(a), and the outstanding rights will be appropriately adjusted in the class(es) and number of securities and price per share of stock subject to such outstanding rights. Such adjustments shall be made by the Board, the determination of which shall be final, binding and conclusive.

(b) In the event of: (1) a dissolution, liquidation or sale of all or substantially all of the assets of the Company, (2) a merger or consolidation in which the Company is not the surviving corporation, or (3) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise or (4) any other capital reorganization in which more than fifty percent (50%) of the securities of the Company entitled to vote are sold or otherwise exchanged, then any surviving corporation may assume outstanding rights or substitute similar rights for those under the Plan. In the event

that no surviving corporation assumes such outstanding rights or substitutes similar rights therefor, participants' accumulated payroll deductions will be used to purchase Common Stock immediately prior to the transaction described above and the participants' rights under the ongoing Offering terminated immediately following such purchase.

13. AMENDMENT OF THE PLAN.

(a) The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 12 relating to adjustments upon changes in stock, no amendment shall be effective unless approved by the stockholders of the Company within twelve (12) months before or after the adoption of the amendment, where the amendment will:

(i) Increase the number of shares reserved for rights under the Plan;

(ii) Modify the provisions as to eligibility for participation in the Plan (to the extent such modification requires stockholder approval in order for the Plan to obtain employee stock purchase plan treatment under Section 423 of the Code or to comply with the requirements of Rule 16b-3 promulgated under the Securities Exchange Act of 1934, as amended ("Rule 16b-3")); or

(iii) Modify the Plan in any other way if such modification requires stockholder approval in order for the Plan to obtain employee stock purchase plan treatment under Section 423 of the Code or to comply with the requirements of Rule 16b-3.

It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide eligible employees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder relating to employee stock purchase plans and/or to bring the Plan and/or rights granted under it into compliance therewith.

(b) Rights and obligations under any rights granted before amendment of the Plan shall not be impaired by any amendment of the Plan, except with the consent of the person to whom such rights were granted, or except as necessary to comply with any laws or governmental regulations, or except as necessary to ensure that the Plan and/or rights granted under the Plan comply with the requirements of Section 423 of the Code.

14. DESIGNATION OF BENEFICIARY.

(a) A participant may file a written designation of a beneficiary who is to receive any shares and cash, if any, from the participant's account under the Plan in the event of such participant's death subsequent to the end of an Offering but prior to delivery to the participant of such shares and cash. In addition, a participant may file a written designation of a beneficiary who is to receive any cash from the participant's account under the Plan in the event of such participant's death during an Offering.

(b) Such designation of beneficiary may be changed by the participant at any time by written notice. In the event of the death of a participant and in the absence of a beneficiary

validly designated under the Plan who is living at the time of such participant's death, the Company shall deliver such shares and/or cash to the executor or administrator of the estate of the participant, or if no such executor or administrator has been appointed (to the knowledge of the Company), the Company, in its sole discretion, may deliver such shares and/or cash to the spouse or to any one or more dependents or relatives of the participant, or if no spouse, dependent or relative is known to the Company, then to such other person as the Company may designate.

15. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Board in its discretion, may suspend or terminate the Plan at any time. No rights may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any rights granted while the Plan is in effect shall not be altered or impaired by suspension or termination of the Plan, except as expressly provided in the Plan or with the consent of the person to whom such rights were granted, or except as necessary to comply with any laws or governmental regulation, or except as necessary to ensure that the Plan and/or rights granted under the Plan comply with the requirements of Section 423 of the Code.

(c) Notwithstanding the foregoing, the Plan shall terminate and no rights may be granted under the Plan after the tenth anniversary of the Effective Date.

16. EFFECTIVE DATE OF PLAN.

The Plan shall become effective on the date on which it is adopted by the Board (the "Effective Date"), but no rights granted under the Plan shall be exercised unless and until the Plan has been approved by the stockholders of the Company within twelve (12) months before or after the date the Plan is adopted by the Board, which date may be prior to the Effective Date.

EXHIBIT 10.13

ISIS PHARMACEUTICALS, INC.

2000 BROAD-BASED EQUITY INCENTIVE PLAN

ADOPTED JANUARY 6, 2000

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ISIS PHARMACEUTICALS, INC.

2000 BROAD-BASED EQUITY INCENTIVE PLAN

ADOPTED JANUARY 6, 2000

1. PURPOSES.

(a) ELIGIBLE STOCK AWARD RECIPIENTS. The persons eligible to receive Stock Awards are the Employees, Directors and Consultants of the Company and its Affiliates.

(b) AVAILABLE STOCK AWARDS. The purpose of the Plan is to provide a means by which eligible recipients of Stock Awards may be given an opportunity to benefit from increases in value of the Common Stock through the granting of the following Stock Awards: (i) Supplemental Stock Options, (ii) stock bonuses and (iii) rights to acquire restricted stock.

(c) GENERAL PURPOSE. The Company, by means of the Plan, seeks to retain the services of the group of persons eligible to receive Stock Awards, to secure and retain the services of new members of this group and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

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

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

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

(d) "COMMITTEE" means a committee of one or more members of the Board appointed by the Board in accordance with subsection 3(c).

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

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

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

(h) "CONTINUOUS SERVICE" means that the Participant's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated.

The Participant's Continuous Service shall not be deemed to have terminated merely because of a change in the capacity in which the Participant renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant's Continuous Service. For example, a change in status from an Employee of the Company to a Consultant of an Affiliate or a Director will not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

(i) "COVERED EMPLOYEE" means the chief executive officer and the four (4) other highest compensated officers of the Company for whom total compensation is required to be reported to shareholders under the Exchange Act, as determined for purposes of Section 162(m) of the Code.

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

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

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

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

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

(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the date of grant, or if the date of grant is not a market trading day, then the last market trading day prior to the date of grant, as reported in The Wall Street Journal or such other source as the Board deems reliable.

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

(o) "NON-EMPLOYEE DIRECTOR" means a Director who either (i) is not a current Employee or Officer of the Company or its parent or a subsidiary, does not receive compensation (directly or indirectly) from the Company or its parent or a subsidiary for services rendered as a consultant or in any capacity other than as a Director (except for an amount as to which disclosure would not be required under Item 404(a) of Regulation S-K promulgated pursuant to the Securities Act ("Regulation S-K")), does not possess an interest in any other transaction as to which disclosure would be required under Item 404(a) of Regulation S-K and is not engaged in a

business relationship as to which disclosure would be required under Item 404(b) of Regulation S-K; or (ii) is otherwise considered a "non-employee director" for purposes of Rule 16b-3.

(p) "OFFICER" means a person who possesses the authority of an "officer" as that term is used in Rule 4460(i)(1)(A) of the Rules of the National Association of Securities Dealers, Inc. For purposes of the Plan, a person in the position of "Vice President" or higher shall be classified as an "Officer" unless the Board or Committee expressly finds that such person does not possess the authority of an "officer" as that term is used in Rule 4460(i)(1)(A) of the Rules of the National Association of Securities Dealers, Inc.

(q) "OPTION" means a Supplemental Stock Option granted pursuant to the Plan.

(r) "OPTIONHOLDER" means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(s) "OUTSIDE DIRECTOR" means a Director who either (i) is not a current employee of the Company or an "affiliated corporation" (within the meaning of Treasury Regulations promulgated under Section 162(m) of the Code), is not a former employee of the Company or an "affiliated corporation" receiving compensation for prior services (other than benefits under a tax qualified pension plan), was not an officer of the Company or an "affiliated corporation" at any time and is not currently receiving direct or indirect remuneration from the Company or an "affiliated corporation" for services in any capacity other than as a Director or (ii) is otherwise considered an "outside director" for purposes of Section 162(m) of the Code.

(t) "PARTICIPANT" means a person to whom a Stock Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(u) "PLAN" means this Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan.

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

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

(x) "STOCK AWARD" means any right granted under the Plan, including an Option, a stock bonus and a right to acquire restricted stock.

(y) "STOCK AWARD AGREEMENT" means a written agreement between the Company and a holder of a Stock Award evidencing the terms and conditions of an individual Stock Award grant. Each Stock Award Agreement shall be subject to the terms and conditions of the Plan.

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

(aa) "TEN PERCENT SHAREHOLDER" means a person who owns (or is deemed to own pursuant to Section 424(d) of the Code) stock possessing more than ten percent (10%) of the total combined voting power of all classes of stock of the Company or of any of its Affiliates.

(bb) "TERMS OF SUPPLEMENTAL STOCK OPTION" means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an individual Option grant. Each Terms of Supplemental Stock Option shall be subject to the terms and conditions of the Plan.

3. ADMINISTRATION.

(a) ADMINISTRATION BY BOARD. The Board shall administer the Plan unless and until the Board delegates administration to a Committee, as provided in subsection 3(c).

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

(i) To determine from time to time which of the persons eligible under the Plan shall be granted Stock Awards; when and how each Stock Award shall be granted; what type or combination of types of Stock Award shall be granted; the provisions of each Stock Award granted (which need not be identical), including the time or times when a person shall be permitted to receive Common Stock pursuant to a Stock Award; and the number of shares of Common Stock with respect to which a Stock Award shall be granted to each such person.

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

(iii) To amend the Plan or a Stock Award as provided in Section 12.

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

(c) DELEGATION TO COMMITTEE.

(i) GENERAL. The Board may delegate administration of the Plan to a Committee or Committees of one (1) or more members of the Board, and the term "Committee" shall apply to any person or persons to whom such authority has been delegated. If administration is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, including the power to delegate to a subcommittee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish the Committee at any time and revest in the Board the administration of the Plan.

(ii) COMMITTEE COMPOSITION WHEN COMMON STOCK IS PUBLICLY TRADED. At such time as the Common Stock is publicly traded, in the discretion of the Board, a Committee may consist solely of two or more Outside Directors, in accordance with Section 162(m) of the Code, and/or solely of two or more Non-Employee Directors, in accordance with Rule 16b-3. Within the scope of such authority, the Board or the Committee may (1) delegate to a committee of one or more members of the Board who are not Outside Directors the authority to grant Stock Awards to eligible persons who are either (a) not then Covered Employees and are not expected to be Covered Employees at the time of recognition of income resulting from such Stock Award or (b) not persons with respect to whom the Company wishes to comply with Section 162(m) of the Code and/or) (2) delegate to a committee of one or more members of the Board who are not Non-Employee Directors the authority to grant Stock Awards to eligible persons who are not then subject to Section 16 of the Exchange Act.

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

4. SHARES SUBJECT TO THE PLAN.

(a) SHARE RESERVE. Subject to the provisions of Section 11 relating to adjustments upon changes in Common Stock, the Common Stock that may be issued pursuant to Stock Awards shall not exceed in the aggregate 1,990,000 shares of Common Stock.

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

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

5. ELIGIBILITY.

(a) ELIGIBILITY FOR SPECIFIC STOCK AWARDS. Stock Awards may be granted to Employees, Directors and Consultants.

(b) RESTRICTIONS ON ELIGIBILITY. Notwithstanding the foregoing, the aggregate number of shares issued pursuant to Stock Awards granted to Officers and Directors cannot exceed forty percent (40%) of the number of shares reserved for issuance under the Plan as determined at the time of each such issuance to an Officer or Director, except that there shall be excluded from this calculation shares issued to Officers not previously employed by the Company pursuant to Stock Awards granted as an inducement essential to such individuals entering into employment contracts with the Company.

(c) CONSULTANTS.

(i) A Consultant shall not be eligible for the grant of a Stock Award if, at the time of grant, a Form S-8 Registration Statement under the Securities Act ("Form S-8") is not

available to register either the offer or the sale of the Company's securities to such Consultant because of the nature of the services that the Consultant is providing to the Company, or because the Consultant is not a natural person, or as otherwise provided by the rules governing the use of Form S-8, unless the Company determines both (i) that such grant (A) shall be registered in another manner under the Securities Act (e.g., on a Form S-3 Registration Statement) or (B) does not require registration under the Securities Act in order to comply with the requirements of the Securities Act, if applicable, and (ii) that such grant complies with the securities laws of all other relevant jurisdictions.

(ii) Form S-8 generally is available to consultants and advisors only if (i) they are natural persons; (ii) they provide bona fide services to the issuer, its parents, its majority-owned subsidiaries or majority-owned subsidiaries of the issuer's parent; and (iii) the services are not in connection with the offer or sale of securities in a capital-raising transaction, and do not directly or indirectly promote or maintain a market for the issuer's securities.

6. OPTION PROVISIONS.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The provisions of separate Options need not be identical, but each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) TERM. The term of an Option shall be the term determined by the Board, either at the time of grant of the Option or as the Option may be amended thereafter.

(b) CONSIDERATION. The purchase price of Common Stock acquired pursuant to an Option shall be paid, to the extent permitted by applicable statutes and regulations, either (i) in cash at the time the Option is exercised or (ii) at the discretion of the Board at the time of the grant of the Option (or subsequently in the case of a Supplemental Stock Option) (1) by delivery to the Company of other Common Stock, (2) according to a deferred payment or other similar arrangement with the Optionholder or (3) in any other form of legal consideration that may be acceptable to the Board. Unless otherwise specifically provided in the Option, the purchase price of Common Stock acquired pursuant to an Option that is paid by delivery to the Company of other Common Stock acquired, directly or indirectly from the Company, shall be paid only by shares of the Common Stock of the Company that have been held for more than six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes). At any time that the Company is incorporated in Delaware, payment of the Common Stock's "par value," as defined in the Delaware General Corporation Law, shall not be made by deferred payment.

In the case of any deferred payment arrangement, interest shall be compounded at least annually and shall be charged at the minimum rate of interest necessary to avoid the treatment as interest, under any applicable provisions of the Code, of any amounts other than amounts stated to be interest under the deferred payment arrangement.

(c) TRANSFERABILITY OF A SUPPLEMENTAL STOCK OPTION. A Supplemental Stock Option shall be transferable to the extent provided in the Terms of Supplemental Stock Option.

If the Supplemental Stock Option does not provide for transferability, then the Supplemental Stock Option shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Optionholder only by the Optionholder. Notwithstanding the foregoing, the Optionholder may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of the death of the Optionholder, shall thereafter be entitled to exercise the Option.

(d) VESTING GENERALLY. The total number of shares of Common Stock subject to an Option may, but need not, vest and therefore become exercisable in periodic installments that may, but need not, be equal. The Option may be subject to such other terms and conditions on the time or times when it may be exercised (which may be based on performance or other criteria) as the Board may deem appropriate. The vesting provisions of individual Options may vary. The provisions of this subsection 6(e) are subject to any Option provisions governing the minimum number of shares of Common Stock as to which an Option may be exercised.

(e) TERMINATION OF CONTINUOUS SERVICE. In the event an Optionholder's Continuous Service terminates (other than upon the Optionholder's death or Disability), the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date three (3) months following the termination of the Optionholder's Continuous Service (or such longer or shorter period specified in the Terms of Supplemental Stock Option), or (ii) the expiration of the term of the Option as set forth in the Terms of Supplemental Stock Option. If, after termination, the Optionholder does not exercise his or her Option within the time specified in the Terms of Supplemental Stock Option, the Option shall terminate.

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

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

(h) DEATH OF OPTIONHOLDER. In the event (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death or (ii) the Optionholder dies within the period (if any) specified in the Terms of Supplemental Stock Option after the termination of the

Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Optionholder's death pursuant to subsection 6(d), but only within the period ending on the earlier of (1) the date eighteen (18) months following the date of death (or such longer or shorter period specified in the Terms of Supplemental Stock Option) or (2) the expiration of the term of such Option as set forth in the Terms of Supplemental Stock Option. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

(i) EARLY EXERCISE. The Option may, but need not, include a provision whereby the Optionholder may elect at any time before the Optionholder's Continuous Service terminates to exercise the Option as to any part or all of the shares of Common Stock subject to the Option prior to the full vesting of the Option. Any unvested shares of Common Stock so purchased may be subject to a repurchase option in favor of the Company or to any other restriction the Board determines to be appropriate. The Company will not exercise its repurchase option until at least six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes) have elapsed following exercise of the Option unless the Board otherwise specifically provides in the Option.

(j) RE-LOAD OPTIONS.

(i) Without in any way limiting the authority of the Board to make or not to make grants of Options hereunder, the Board shall have the authority (but not an obligation) to include as part of any Terms of Supplemental Stock Option a provision entitling the Optionholder to a further Option (a "Re-Load Option") in the event the Optionholder exercises the Option evidenced by the Terms of Supplemental Stock Option, in whole or in part, by surrendering other shares of Common Stock in accordance with this Plan and the terms and conditions of the Terms of Supplemental Stock Option. Unless otherwise specifically provided in the Option, the Optionholder shall not surrender shares of Common Stock acquired, directly or indirectly from the Company, unless such shares have been held for more than six (6) months (or such longer or shorter period of time required to avoid a charge to earnings for financial accounting purposes).

(ii) Any such Re-Load Option shall (1) provide for a number of shares of Common Stock equal to the number of shares of Common Stock surrendered as part or all of the exercise price of such Option; (2) have an expiration date which is the same as the expiration date of the Option the exercise of which gave rise to such Re-Load Option; and (3) have an exercise price which is equal to one hundred percent (100%) of the Fair Market Value of the Common Stock subject to the Re-Load Option on the date of exercise of the original Option. Notwithstanding the foregoing, a Re-Load Option shall be subject to the same exercise price and term provisions heretofore described for Options under the Plan.

(iii) There shall be no Re-Load Options on a Re-Load Option. Any such Re-Load Option shall be subject to the availability of sufficient shares of Common Stock under subsection 4(a) and shall be subject to such other terms and conditions as the Board may

determine which are not inconsistent with the express provisions of the Plan regarding the terms of Options.

7. PROVISIONS OF STOCK AWARDS OTHER THAN OPTIONS.

(a) STOCK BONUS AWARDS. Each stock bonus agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of stock bonus agreements may change from time to time, and the terms and conditions of separate stock bonus agreements need not be identical, but each stock bonus agreement shall include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) CONSIDERATION. A stock bonus may be awarded in consideration for past services actually rendered to the Company or an Affiliate for its benefit.

(ii) VESTING. Shares of Common Stock awarded under the stock bonus agreement may, but need not, be subject to a share repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board.

(iii) TERMINATION OF PARTICIPANT'S CONTINUOUS SERVICE. In the event a Participant's Continuous Service terminates, the Company may reacquire any or all of the shares of Common Stock held by the Participant which have not vested as of the date of termination under the terms of the stock bonus agreement.

(iv) TRANSFERABILITY. Rights to acquire shares of Common Stock under the stock bonus agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the stock bonus agreement, as the Board shall determine in its discretion, so long as Common Stock awarded under the stock bonus agreement remains subject to the terms of the stock bonus agreement.

(b) RESTRICTED STOCK AWARDS. Each restricted stock purchase agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of the restricted stock purchase agreements may change from time to time, and the terms and conditions of separate restricted stock purchase agreements need not be identical, but each restricted stock purchase agreement shall include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

(i) PURCHASE PRICE. The purchase price under each restricted stock purchase agreement shall be such amount as the Board shall determine and designate in such restricted stock purchase agreement. The purchase price shall not be less than eighty-five percent (85%) of the Common Stock's Fair Market Value on the date such award is made or at the time the purchase is consummated.

(ii) CONSIDERATION. The purchase price of Common Stock acquired pursuant to the restricted stock purchase agreement shall be paid either: (i) in cash at the time of purchase; (ii) at the discretion of the Board, according to a deferred payment or other similar arrangement with the Participant; or (iii) in any other form of legal consideration that may be

acceptable to the Board in its discretion; provided, however, that at any time that the Company is incorporated in Delaware, then payment of the Common Stock's "par value," as defined in the Delaware General Corporation Law, shall not be made by deferred payment.

(iii) VESTING. Shares of Common Stock acquired under the restricted stock purchase agreement may, but need not, be subject to a share repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board.

(iv) TERMINATION OF PARTICIPANT'S CONTINUOUS SERVICE. In the event a Participant's Continuous Service terminates, the Company may repurchase or otherwise reacquire any or all of the shares of Common Stock held by the Participant which have not vested as of the date of termination under the terms of the restricted stock purchase agreement.

(v) TRANSFERABILITY. Rights to acquire shares of Common Stock under the restricted stock purchase agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the restricted stock purchase agreement, as the Board shall determine in its discretion, so long as Common Stock awarded under the restricted stock purchase agreement remains subject to the terms of the restricted stock purchase agreement.

8. COVENANTS OF THE COMPANY.

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

(b) SECURITIES LAW COMPLIANCE. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained.

9. USE OF PROCEEDS FROM STOCK.

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

10. MISCELLANEOUS.

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

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

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

(d) INVESTMENT ASSURANCES. The Company may require a Participant, as a condition of exercising or acquiring Common Stock under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Participant is acquiring Common Stock subject to the Stock Award for the Participant's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

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

11. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) CAPITALIZATION ADJUSTMENTS. If any change is made in the Common Stock subject to the Plan, or subject to any Stock Award, without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the Plan pursuant to subsection 4(a), and the outstanding Stock Awards will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) CHANGE IN CONTROL--DISSOLUTION OR LIQUIDATION. In the event of a dissolution or liquidation of the Company, then all outstanding Stock Awards shall terminate immediately prior to such event.

(c) CHANGE IN CONTROL - ASSET SALE, MERGER, CONSOLIDATION OR REVERSE MERGER. In the event of (i) a sale, lease or other disposition of all or substantially all of the assets of the Company, (ii) a merger or consolidation in which the Company is not the surviving corporation or (iii) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, then any surviving corporation or acquiring corporation shall assume any Stock Awards outstanding under the Plan or shall substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction described in this subsection 11(c) for those outstanding under the Plan). In the event any surviving corporation or acquiring corporation refuses to assume such Stock Awards or to substitute similar stock awards for those outstanding under the Plan, then with respect to Stock Awards held by Participants whose Continuous Service has not terminated, the vesting of such Stock Awards (and, if applicable, the time during which such Stock Awards may be exercised) shall be accelerated in full, and the Stock Awards shall terminate if not exercised (if applicable) at or prior to such event. With respect to any other Stock Awards outstanding under the Plan, such Stock Awards shall terminate if not exercised (if applicable) prior to such event.

12. AMENDMENT OF THE PLAN AND STOCK AWARDS.

(a) AMENDMENT OF PLAN. The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 11 relating to adjustments upon changes in Common Stock, no amendment shall be effective unless approved by the shareholders of the Company to the extent shareholder approval is necessary to satisfy the requirements of Section 422 of the Code, Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) SHAREHOLDER APPROVAL. The Board may, in its sole discretion, submit any other amendment to the Plan for shareholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of Section 162(m) of the Code and the regulations thereunder regarding the exclusion of performance-based compensation from the limit on corporate deductibility of compensation paid to certain executive officers.

(c) CONTEMPLATED AMENDMENTS. It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide eligible Employees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder and/or to bring the Plan and/or Options into compliance therewith.

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

(e) AMENDMENT OF STOCK AWARDS. The Board at any time, and from time to time, may amend the terms of any one or more Stock Awards; provided, however, that the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the Participant and (ii) the Participant consents in writing.

13. TERMINATION OR SUSPENSION OF THE PLAN.

(a) PLAN TERM. The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on the day before the tenth (10th) anniversary of the date the Plan is adopted by the Board or approved by the shareholders of the Company, whichever is earlier. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

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

14. EFFECTIVE DATE OF PLAN.

The Plan shall become effective on January 6, 2000.

15. CHOICE OF LAW.

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

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EXHIBIT 10.14

Optionee: _____ Date: _____

ISIS PHARMACEUTICALS, INC.
2000 PLAN SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 2000 Broad-Based Equity Incentive 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:_____

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting)(1)
_____	_____
_____	_____
_____	_____
_____	_____

Exercise Price Per Share: (2) _____ Expiration Date:(3)
Percentage of Full-Time Work: 100% ------

Isis Pharmaceuticals, Inc.

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

Address:

OPTIONEE:

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 acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) After the first year, the option will vest monthly with 2.08% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, a reduced number of shares will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. Increases of work percentage up to but not in excess of the Percentage of Full Time Work specified above will result in a corresponding increase in the percentage of shares vesting. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

(2) Not less than 85% of the fair market value of the Common Stock on the date of grant of this option.

(3) Less than 10 years from the date of grant of this option.

ATTACHMENT I
TERMS OF SUPPLEMENTAL STOCK OPTION

The grant hereunder is in connection with and in furtherance of the Company's 2000 Broad-Based Equity Incentive Plan (the "Plan") for participation of the Company's employees (including officers), directors or consultants and is intended to comply with the provisions of Rule 701 promulgated by the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "Act").

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Supplemental Stock Option Agreement. Subject to the limitations contained herein, this option is exercisable with respect to each installment indicated in the Vesting Schedule set forth on the first page of the Supplemental Stock Option Agreement on or after the date of vesting applicable to such installment.

2. Notwithstanding any provision in the Plan to the contrary, in the event of a Change in Control (as defined below) then the vesting and exercisability of this stock option will be accelerated in full; provided, however, that if such potential acceleration of the vesting and exercisability of this stock option would cause a contemplated Change in Control transaction that would otherwise be eligible to be accounted for as a "pooling-of-interests" transaction to become ineligible for such accounting treatment under generally accepted accounting principles as determined by the Company's independent certified public accountants prior to the Change of Control, such acceleration will not occur.

For purposes of this paragraph 2 only, Change in Control means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving corporation and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

3. (a) The Exercise Price of this option is set forth on the first page of the Supplemental Stock Option Agreement.

(b) Payment of the exercise price per share is due in full in cash (including check) upon exercise of all or any part of each installment which has become exercisable by you.

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

5. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

6. The term of this option commences on the date hereof and, unless sooner terminated as set forth below or in the Plan, terminates on the Expiration Date. This option shall terminate prior to the expiration of its term as follows: 3 months after the termination of your employment with the Company or an Affiliate of the Company (as defined in the Plan) for any reason or for no reason unless:

(a) such termination of employment is due to your Disability, in which event the option shall terminate on the earlier of the termination date set forth above or 1 year following such termination of employment;

(b) such termination of employment is due to your death, in which event the option shall terminate on the earlier of the termination date set forth above or 18 months after your death; or

(c) during any part of such 3 month period the option is not exercisable solely because of the condition set forth in paragraph 5 above, in which event the option shall not terminate until the earlier of the termination date set forth above or until it shall have been exercisable for an aggregate period of 3 months after the termination of employment; or

(d) exercise of the option within 3 months after termination of your employment with the Company or with an Affiliate would result in liability under Section 16(b) of the Securities Exchange Act of 1934, in which case the option will terminate on the earlier of the termination date set forth above, the 10th day after the last date upon which exercise would result in such liability or 6 months and 10 days after the termination of your employment with the Company or an Affiliate.

However, this option may be exercised following termination of employment only as to that number of shares as to which it was exercisable on the date of termination of employment under the provision of paragraph 1 of this option.

7. (a) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours.

(b) By exercising this option you agree that:

(i) the Company may require you to enter an arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise.

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

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

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

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

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

9. This option is not an employment contract and nothing in this option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company, or of the Company to continue your employment with the Company. In the event that this option is granted to you in connection with the performance of services as a consultant or director, references to employment, employee and similar terms shall be deemed to include the performance of services as a consultant or a director, as the case may be, provided, however, that no rights as an employee shall arise by reason of the use of such terms.

10. Any notices provided for in this option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified on the attached or at such other address as you hereafter designate by written notice to the Company.

11. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 6 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of this option and those of the Plan, the provisions of the Plan shall control.

Attachments: 2000 Broad-Based Equity Incentive Plan
Notice of Exercise

EXHIBIT 10.15

Optionee: _____ Date: _____

ISIS PHARMACEUTICALS, INC.
SUPPLEMENTAL STOCK OPTION AGREEMENT
(DIRECTOR)

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 2000 Broad-Based Equity Incentive 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:_____

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting)
_____	_____
_____	_____
_____	_____
_____	_____

Exercise Price Per Share: _____ (1)

Expiration Date: _____ (2)

Percentage of Full-Time Work: 100%

Isis Pharmaceuticals, Inc.

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

Optionee: _____
Address:

OPTIONEE:

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 acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) Not less than 85% of the fair market value of the Common Stock on the date of grant of this option.

(2) Less than 10 years from the date of grant of this option.

ATTACHMENT I
TERMS OF SUPPLEMENTAL STOCK OPTION
(DIRECTOR)

The grant hereunder is in connection with and in furtherance of the Company's 2000 Broad-Based Equity Incentive Plan (the "Plan") for participation of the Company's employees (including officers), directors or consultants and is intended to comply with the provisions of Rule 701 promulgated by the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "Act").

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Supplemental Stock Option Agreement. Subject to the limitations contained herein, this option is exercisable with respect to each installment indicated in the Vesting Schedule set forth on the first page of the Supplemental Stock Option Agreement on or after the date of vesting applicable to such installment.

2. Notwithstanding any provision in the Plan to the contrary, in the event of a Change in Control (as defined below) then the vesting and exercisability of this stock option will be accelerated in full; provided, however, that if such potential acceleration of the vesting and exercisability of this stock option would cause a contemplated Change in Control transaction that would otherwise be eligible to be accounted for as a "pooling-of-interests" transaction to become ineligible for such accounting treatment under generally accepted accounting principles as determined by the Company's independent certified public accountants prior to the Change of Control, such acceleration will not occur.

For purposes of this paragraph 2 only, Change in Control means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving corporation and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

3. (a) The Exercise Price of this option is set forth on the first page of the Supplemental Stock Option Agreement.

(b) Payment of the exercise price per share is due in full in cash (including check) upon exercise of all or any part of each installment which has become exercisable by you.

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

5. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

6. The term of this option commences on the date hereof and, unless sooner terminated as set forth below or in the Plan, terminates on the Expiration Date. This option shall terminate prior to the expiration of its term as follows: 3 months after the termination of your service as a Director with the Company or an Affiliate of the Company (as defined in the Plan) for any reason or for no reason unless:

(a) such termination of service is due to your Disability, in which event the option shall

terminate on the earlier of the termination date set forth above or 1 year following such termination of service;

(b) such termination of service is due to your death, in which event the option shall terminate on the earlier of the termination date set forth above or 18 months after your death; or

(c) during any part of such 3 month period the option is not exercisable solely because of the condition set forth in paragraph 5 above, in which event the option shall not terminate until the earlier of the termination date set forth above or until it shall have been exercisable for an aggregate period of 3 months after the termination of service; or

(d) exercise of the option within 3 months after termination of your service with the Company or with an Affiliate would result in liability under Section 16(b) of the Securities Exchange Act of 1934, in which case the option will terminate on the earlier of the termination date set forth above, the 10th day after the last date upon which exercise would result in such liability or 6 months and 10 days after the termination of your service with the Company or an Affiliate.

However, this option may be exercised following termination of service only as to that number of shares as to which it was exercisable on the date of termination of service under the provision of paragraph 1 of this option.

7. (a) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours.

(b) By exercising this option you agree that:

(i) the Company may require you to enter an arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise.

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

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

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

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

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

9. This option is not a service contract and nothing in this option shall be deemed to create in any way whatsoever any obligation on your part to continue as a Director of the Company, or of the Company to continue your service with the Company. In the event that this option is granted to you in connection with the performance of services as a consultant or director, references to service, employee and similar terms shall be deemed to include the performance of services as a consultant or a director, as the case may be, provided, however, that no rights as an employee shall arise by reason of the use of such terms.

10. Any notices provided for in this option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified on the attached or at such other address as you hereafter designate by written notice to the Company.

11. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 6 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the

provisions of this option and those of the Plan, the provisions of the Plan shall control.

Attachments: 2000 Broad-Based Equity Incentive Plan
Notice of Exercise

EXHIBIT 10.16

January 11, 2000

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Isis Pharmaceuticals, Inc.
2292 Faraday Ave.
Carlsbad, CA 92008

Dear

Isis Pharmaceuticals, Inc. ("Isis") is pleased to offer you certain severance benefits in light of your contributions to Isis. As Isis has no policy or procedure requiring such benefits, we request that you keep the terms and conditions of this letter agreement confidential.

In the event that your employment is terminated without "cause" (as defined herein) by Isis on or before December 31, 2001 (the "Severance Period"), you will be eligible to receive a severance payment equal to a minimum of six (6) months of your then current base salary, less payroll deductions and withholdings. For purposes of this letter agreement, "cause" will be defined as follows: (i) engaging or in any manner participating in any activity which is competitive with or intentionally injurious to Isis or which violates any provision of the Proprietary Information and Inventions Agreement; (ii) commission of any fraud against Isis or use or appropriation for personal use or benefit of any funds or properties of Isis not authorized by the Company to be so used or appropriated; (iii) conviction of a crime involving dishonesty or moral turpitude; (iv) conduct by you which in the good faith and reasonable determination of the Company demonstrates gross unfitness to serve in your then current capacity at Isis. In order to be eligible to receive the severance payments described herein, you will be required to execute an Employee Separation Agreement substantially in the form attached hereto as Exhibit A.

In the event that your employment is terminated during the Severance Period as a result of a reduction of the Company's workforce or you elect to terminate your employment with Isis as a result of substantial change in your primary job duties, your severance payment shall be increased such that you receive a total payment equal to twelve (12) months of your then current base salary, less payroll deductions and withholdings.

In the event that your employment is terminated by Isis during the Severance Period as a result of a Change in Control (as defined herein), your severance payment shall be increased such that you receive a total of twenty-four (24) months of your then current base salary, less payroll deductions and withholdings. For purposes of this letter agreement, Change in Control will be defined as follows: (i) a sale of all or substantially all of the assets of Isis; (ii) a merger or consolidation in which Isis is not the surviving corporation and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which Isis is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by Isis or subsidiary of Isis or other entity controlled by Isis) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

Please keep in mind that this letter agreement is not intended to change your status as an at-will employee with Isis. As with all employees at Isis, you or Isis may terminate your employment at any time, for any reason whatsoever, with or without cause or advance notice subject to the provisions set forth herein.

If you have any questions or comments regarding the terms and conditions of this letter, please do not hesitate to contact me.

Very truly yours,

Isis Pharmaceuticals, Inc.

Patricia M. Lowenstam
Vice President, Human Resources

PML/jk

attachment

SEVERANCE AGREEMENT

SCHEDULE

NAMES OF EXECUTIVE OFFICERS WHO ARE PARTIES TO THE SEVERANCE AGREEMENT
Stanley T. Crooke
B. Lynne Parshall
Debby Jo Blank
C. Frank Bennett
David J. Ecker
Patricia Lowenstam

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-3 No. 33-75068, 33-96138, and 333-71911 and Form S-8 No. 33-51236, 33-42970, 33-42356, 33-54840, 33-58450, 33-43330, 33-75150, 33-90780, 333-05825, and 333-55683) of Isis Pharmaceuticals, Inc. of our report dated January 28, 2000, except for paragraph 3 of Note 8, as to which the date is March 8, 2000 with respect to the financial statements of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 1999.

ERNST & YOUNG LLP

San Diego, California
March 24, 2000

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This schedule contains summary financial information derived from the Company's Balance Sheet as of December 31, 1999 and Statements of Operations for the Year Ended December 31, 1999 and is qualified in its entirety by reference to such financial statements.

1,000

YEAR
DEC-31-1999
JAN-01-1999
DEC-31-1999
35,296
17,543
5,429
0
0
59,197
23,945
0
103,107
14,984
87,254
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0
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837
103,107
0
33,925
0
0
76,984
0
11,424
(59,645)
0
(59,645)
0
0
0
(59,645)
(2.08)
(2.08)