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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K/A

AMENDMENT NO. 2

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 1998

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 $297,565,000 as of February 26, 1999.*

The number of shares of common stock outstanding as of February 26, 1999 was 27,169,623.

DOCUMENTS INCORPORATED BY REFERENCE
(TO THE EXTENT INDICATED HEREIN)

Registrant's definitive Proxy Statement which will be filed on or before April 13, 1999 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 21, 1999 is incorporated by reference into Part III of this Report.

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- - Excludes 2,501,021 shares of common stock held by directors and officers and stockholders whose beneficial ownership exceeds 10 percent of the shares outstanding at February 26, 1999. 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.

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This Form 10-K/A contains forward-looking statements regarding the Company's business, 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/A. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this Form 10-K/A 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 leader in the discovery and development of a new class of drugs based on antisense technology. With antisense technology, we believe we can design drugs that are safer and more effective than traditional drugs. We combine our expertise in molecular and cellular biology with antisense drug discovery techniques to design drugs to fight a wide range of diseases, including infectious and inflammatory diseases and cancer. In 1998, our first drug was approved for commercial sale. In addition, we have five antisense compounds in human clinical trials, with additional compounds arising out of our broad research program in preclinical development.

Through our expertise in medicinal chemistry and RNA structure and function, we have also developed a proprietary RNA-targeting drug discovery program. This program is being run by our Ibis Therapeutics division and allows us to use genomic information to identify novel structural targets and to quickly create and screen, as potential drugs, large libraries of small molecule compounds designed to inhibit those targets.

In August 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 by the FDA. 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 1998, we also filed an application for European marketing approval for Vitravene(TM). That application is presently being reviewed by the European regulatory authorities.

This chart represents the pipeline of Isis products currently in preclinical and clinical development:

ISIS DEVELOPMENT PIPELINE

ISIS 2302 is in clinical trials to treat a variety of inflammatory diseases and conditions. ISIS 2302 targets intercellular adhesion molecule-1, ICAM-1, which is involved in many such diseases. We are testing ISIS 2302 against Crohn's disease, psoriasis, ulcerative colitis, renal transplant rejection and asthma. In a Phase II study of patients with Crohn's disease, an encouraging number of patients receiving ISIS 2302 had their symptoms improve. A statistically significant (p=0.0001) number were also able to reduce, and for some patients completely eliminate, their steroid use, the most common treatment for Crohn's disease. Because of these positive results, we began a pivotal quality trial of ISIS 2302 in Crohn's disease in 1997. The 300 patient,

pivotal quality trial in Crohn's disease should be completed in late 1999. We continue to be optimistic about the potential of ISIS 2302 to treat Crohn's disease. Toward that end, we are completing the pivotal trial and plan to move expeditiously toward a regulatory submission, assuming that the data are supportive.

The kidney transplant Phase II trial of ISIS 2302 is progressing, and we anticipate completion in mid-1999. We will make the data available after completion of the trial. We are also pursuing development of ISIS 2302 as a topical treatment for psoriasis, as an enema formulation for treatment of ulcerative colitis, and as an aerosol formulation for treatment of asthma. We intend to initiate clinical trials in as many of these indications as resources permit in the near term.

We recently completed the analysis of the Phase II, 43 patient study of ISIS 2302 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 3521 is in 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 targets protein kinase C-X or PKC-X, a protein associated with abnormal cell growth. We are developing ISIS 3521 as part of our collaboration with Novartis. In Phase I trials, ISIS 3521 stabilized disease, reduced tumor mass and reduced tumor markers in a number of patients with ovarian cancer, lymphoma and lung cancer. In those trials, ISIS 3521 caused no significant side effects. We have been conducting studies of ISIS 3521 in combination with chemotherapy agents commonly used against a variety of tumors.

ISIS 5132 is also in 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 targets C-raf kinase, another type of protein associated with abnormal cell growth. We are also developing ISIS 5132 as part of our collaboration with Novartis. 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 caused no significant side effects. We have also been conducting studies of ISIS 5132 in combination with chemotherapy agents commonly used against a variety of tumors.

ISIS 2503 has completed Phase I clinical trials as an anticancer agent. This compound inhibits expression of Ha-ras, another protein associated with cancer. Phase II trials will begin in early 1999. The Phase II trial will be conducted in patients with a variety of solid tumors. We will initiate clinical trials of ISIS 2503 in combination with conventional chemotherapy in the first half of 1999.

ISIS 13312 is in Phase I clinical trials to treat CMV retinitis in AIDS patients. ISIS 13312 is being evaluated in a small, open label, dose ranging study in patients with advanced CMV retinitis. We have designed a prudent development plan for this drug as a follow-on product to Vitravene(TM). Its future will depend on the progress of treatments for AIDS and the market need. This initial study should be completed in 1999.

We also have several antisense compounds in preclinical development, some of which incorporate novel chemical classes that may provide improved potency, reduced side effects, less frequent dosing and the possibility of oral delivery. These include a compound inhibiting proteins critical for Hepatitis C gene expression, inhibitors of inflammatory targets TNF-X and CD49d, and improved antisense inhibitors of ICAM-1. Isis is also studying improved versions of C-raf kinase and PKC-X in preclinical models.

We have many research programs that use both antisense and RNA-targeting drug discovery technologies to identify compounds that inhibit molecular targets associated with other diseases. Our antisense research programs focus on targets associated with infectious, inflammatory, cardiovascular and metabolic diseases and cancer. They combine our expertise in molecular biology and drug discovery with antisense tools to enable rapid identification of potent inhibitors of disease causing proteins. We are then able to apply our medicinal chemistry expertise to specifically tailor a compound to the particular disease indication targeted.

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. Our RNA-targeting program is focused on identifying the structural elements of RNA targets which are important in initiating or maintaining diseases, and designing compounds that interfere with the function of these RNA targets, including those involved in viral and bacterial infections. This program is also focused on designing small molecules to block the production or function of cell adhesion molecules.

We have successfully leveraged our technology through supportive corporate collaborations with Novartis, Boehringer Ingelheim, CIBA Vision, Merck & Co., Zeneca Pharmaceuticals and Abbott Laboratories. 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.

Our antisense target validation program utilizes antisense technology to streamline the identification, functionalization, and validation of the role novel gene targets play in human disease. This year, we established our first antisense target validation collaboration with Abbott Laboratories. In this collaboration, we are using our proprietary rapid throughput screening technology to design, synthesize, screen and characterize inhibitors of Abbott's novel gene targets. Abbott will use these antisense inhibitors to identify the role of the gene target and its function in disease. This information will enable Abbott to prioritize these novel targets for its drug discovery programs.

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. In conjunction with obtaining approval of Vitravene(TM), we successfully passed the manufacturing pre-approval inspection by the FDA. Under the terms of our agreement with CIBA Vision, Isis will manufacture all of the commercial supplies of Vitravene(TM).

ISIS DRUG DISCOVERY AND DEVELOPMENT

The goal of drug discovery is to create chemical compounds that can help fight or prevent disease. We founded our antisense and RNA-targeting drug discovery programs on our expertise in medicinal chemistry, RNA biochemistry and molecular and cellular biology. We have assembled a team of scientists skilled in these core disciplines to apply the technology to both of our drug discovery platforms. Once a drug is designed, our significant expertise in medicinal chemistry enables us to specifically tailor the chemical structure of the lead compound for its intended use.

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 six 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.

RNA-targeting Drug Discovery

Ibis Therapeutics is our program to discover low molecular weight, 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 (up to 500 compounds) can be screened in the presence of up to 10 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 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 long-term goal for Ibis is that it 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.

ANTISENSE TARGET VALIDATION

With the establishment of our first target validation partnership with Abbott Laboratories, and with the potential for additional partnerships, we are establishing antisense as an essential drug discovery tool for the genomics age.

Our Antisense Target Validation program produces highly specific antisense inhibitors of novel gene products. These 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 drug used to validate the target can be rapidly developed as a human therapeutic.

With antisense, we can rapidly identify active sites on a gene when only a small fragment of the gene sequence is known. The rapid throughput design, synthesis and optimization of antisense oligonucleotides dramatically reduces the time required to validate novel targets. Once we know the mRNA sequence, an antisense inhibitor can be synthesized in just a few days and be ready for screening in vitro or in vivo. It can take a few more days to identify a lead compound and, if needed, about a week to optimize the lead. This accelerated process contrasts dramatically with the months required for small molecule lead generation.

To take advantage of the use of antisense in functional genomics, we have established 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. In addition to amassing a valuable bank of potential product leads, we are also expanding our antisense proprietary position. As rapidly as these gene targets can be produced, we can also file patent applications.

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

CLINICAL DEVELOPMENT

COMPOUND	TARGET	DISEASE INDICATION	DEVELOPMENT STATUS(1)	COMMERCIAL RIGHTS
Vitravene	CMV	Retinitis	Approved for marketing in the U.S. European market application under review.	Isis/CIBA Vision(2)
ISIS 2302	ICAM-1	Crohn's disease	Pivotal trial	Isis/Boehringer Ingelheim(3)
		Kidney transplant rejection	Phase II	
		Psoriasis (topical)	IND candidate	
		Ulcerative colitis (enema)	IND candidate	
ISIS 3521	PKC-(LOGO)	Cancer	Phase II	Novartis(4)
ISIS 5132	C-raf kinase	Cancer	Phase II	Novartis(4)
ISIS 2503	Ha-ras	Cancer	Phase II	Isis
ISIS 13312	CMV	Retinitis	Phase I/II	Isis/CIBA Vision(2)
ISIS 14803	HCV	Hepatitis C	IND Candidate	Isis
	TNF-(LOGO)	Inflammation	Preclinical	Isis
	CD49d	Inflammation	Preclinical	Isis

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(1) An "IND candidate" is a compound for which IND-enabling toxicology and pharmacokinetic studies have been initiated and IND preparation has begun. "Preclinical" means that a lead compound has been identified which Isis has determined is a candidate for commercial development. Preclinical development activities include pharmacology, toxicology and pharmacokinetic testing in preclinical models (in vitro and animal), formulation work and manufacturing scale-up in preparation for submission of the necessary data to comply with applicable regulations prior to commencement of human testing. In some cases, we are developing compounds, such as Vitravene(TM), to treat certain diseases for which no adequately predictive animal efficacy model exists. As a result, we may only conduct in vitro efficacy studies for such compounds, prior to testing the efficacy of the compounds in humans, and drug candidates for these diseases must progress to Phase II human clinical trials before we will have evidence of in vivo efficacy for such compounds. Preclinical development includes studies which may provide preliminary evidence of a compound's safety in animals but which may not, without additional testing, be sufficient to commence human clinical trials. Results obtained in preclinical studies are not necessarily indicative of results that will be obtained in later stages of preclinical development or in human clinical testing.

(2) CIBA Vision has the exclusive right to distribute fomivirsen. CIBA Vision also has an option to acquire the exclusive license to market and distribute ISIS 13312.

(3) Boehringer Ingelheim and we are co-developing ISIS 2302 and may develop other cell adhesion compounds. The companies will split the profits equally if ISIS 2302 is commercialized.

(4) We are developing ISIS 3521 and ISIS 5132 under the direction of Novartis and at Novartis' expense, and may co-develop second generation compounds as well.

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. Nevertheless, because of side effects and poor compliance with prescribed treatment regimens, many of the approximately 1 million HIV infected individuals will probably ultimately progress to and through the advanced stages of AIDS. A significant percentage of these AIDS patients may develop CMV retinitis. The drugs that are available now for CMV retinitis, other than fomivirsen, have limitations, including the creation of viral resistance. 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. In order to begin and maintain IV treatment with ganciclovir and foscarnet, patients require daily administrations of the drug through lines that are placed permanently in the veins to allow easy access to the blood stream. Ganciclovir, foscarnet and cidovovir are associated with significant toxic effects to the body. Oral ganciclovir is approved for preventive treatment and maintenance therapy, but is less effective than IV ganciclovir and still carries significant side effects. The ganciclovir intraocular implant is a small disk that is surgically implanted in the patient's eye and provides local sustained release of the drug for up to eight months. However, this treatment is associated with impaired vision for two to four weeks after implantation in most patients, and the implant itself has also been associated with an increased incidence of retinal detachment that can result in permanent blindness. There is a 12-18% chance of retinal detachment after the first implant and a near 30% chance following a second or third implant. Cidofovir is administered intravenously less frequently than ganciclovir or foscarnet: weekly for the initial therapy and every two weeks for maintenance therapy. Cidofovir is also associated with significant toxicities, particularly to the kidney. For that reason, the patient must take other drugs and follow strict safety measures over a period of approximately 12 hours to manage toxicities.

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 distribution partner for this drug, launched Vitravene(TM) in November 1998. In 1998 we also filed an application for European marketing approval. That application is currently being reviewed by the European regulatory authorities.

As CMV retinitis patients are living longer with their disease due to improvements in the management of HIV infection and AIDS, there is increasing need for more CMV retinitis treatment options, particularly ones with novel mechanisms of action such as Vitravene(TM). Local therapy with Vitravene(TM) could provide therapeutic benefit without significant side effects or the need for intravenous treatments. Treatment with oral ganciclovir or other systemic CMV therapies in combination with Vitravene(TM) could be reserved for patients who show evidence of the disease in other organs. Approximately one-third of the patients diagnosed with CMV retinitis could develop systemic CMV disease, but, in general, these disease manifestations are short-lived and require short courses of therapy.

In July 1997, the Company entered into an agreement with CIBA Vision Corporation (a Novartis subsidiary) granting CIBA Vision exclusive worldwide distribution rights for Vitravene(TM). See "Collaborative Agreements -- CIBA Vision."

ISIS 13312. ISIS 13312, a second generation compound, is based on novel, improved antisense chemistry and is being tested in a Phase I clinical trial as a local treatment for CMV retinitis in AIDS patients. Based on the results of preclinical studies, ISIS 13312 appears to be less toxic and more stable than

Vitravene. ISIS 13312 is being evaluated in a small, open label, dose ranging study in patients with advanced CMV retinitis. We have designed a prudent development plan for this drug as a follow-on product to Vitravene. Its future will depend upon the progress of treatments for AIDS and the market need. This initial study should be completed in 1999. CIBA Vision has an option to market and distribute ISIS 13312 exclusively worldwide. See "Collaborative Agreements -- CIBA Vision."

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 Americans are infected with HCV and 8,000-10,000 people are expected to die from this disease each year. Interferon -- a therapy 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. Upon binding to the complementary target sequence, ISIS 14803 inhibits expression of HCV proteins required for viral replication. The ability of ISIS 14803 to inhibit HCV gene expression in cell culture and in a novel in vivo mouse model of HCV gene expression demonstrates the potential of this compound as a drug development candidate. Preclinical toxicology and pharmacokinetics studies of ISIS 14803 will begin in early 1999.

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.

Some cell adhesion molecules are expressed on the surface of endothelial cells which line the blood vessels of the body during periods of heightened inflammatory or immune system response. These adhesion molecules act as anchors for various types of immune cells circulating in the blood. Once the immune cells are anchored to the endothelial cells by the cell adhesion molecules, these immune cells can migrate between the endothelial cells, leave the blood vessels and travel into tissues and organs where they can cause inflammation. Left unchecked, these processes can result in acute and chronic tissue damage and disease. Current anti-inflammatory agents and drugs that suppress the immune system decrease the symptoms of inflammation but do little to change the course of the underlying disease, or do so at the risk of substantial toxicity. However, a drug that stops the production of cell adhesion molecules may prevent the migration of immune cells from the blood vessels into tissue and therefore modify the disease process with a more acceptable toxicity profile than do currently available therapies.

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), vascular cell adhesion molecule 1 (VCAM-1) and platelet endothelial cell adhesion molecule 1 (PECAM-1). We are currently evaluating those lead compounds in inflammatory disease models.

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-(LOGO) (TNF-(LOGO)), 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.

In 1995, Boehringer Ingelheim and we agreed to combine our respective programs in the area of cell adhesion to form a jointly managed and funded effort. This partnership combines Boehringer Ingelheim's significant expertise in cell adhesion biology and its small molecule and monoclonal antibody-based drug discovery efforts, including its state-of-the-art analysis technology, with our antisense and combinatorial drug discovery programs. The collaboration uses these multiple drug discovery programs to identify compounds that limit the disease-related functions of cell adhesion molecules.

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 initiated Phase II trials in five disease indications: rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis and prevention of renal transplant rejection. The Phase II studies involve 20 to 40 patients each and, in general, are randomized and placebo-controlled. We are choosing indications for further development of ISIS 2302 based on results from these studies.

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 500,000 people in North America and Europe worldwide are afflicted with Crohn's disease. In a randomized, double-blinded, placebo-controlled 20-patient Phase II study of patients with Crohn's disease, 15 patients were treated with ISIS 2302 and 5 patients received a placebo. ISIS 2302 was administered every other day for 26 days (13 doses) by 2-hour intravenous infusion. At the end of the one-month treatment period, 7 of 15 patients treated with ISIS 2302 experienced disease remission (measured by a Crohn's Disease Activity Index score of below 150) compared to zero patients in remission in the placebo group. The duration of the remissions was prolonged, with 5 of 7 remitting patients still in remission at the end of the 6-month trial. Results of this study also showed a statistically significant lowering of steroid use in the ISIS 2302 treated group compared to the placebo treated group. The results also showed favorable trends both in the Endoscopic Index of Severity (EIS), based on colonoscopic examination, and in the Inflammatory Bowel Disease Questionnaire (IBDQ), a quality of life scale. Based on the results of this study, Boehringer Ingelheim and we decided to initiate a pivotal quality trial of ISIS 2302 in Crohn's disease. That 300 patient trial is progressing. It should be completed late in 1999. At that point, we and Boehringer Ingelheim will determine the pace and scope of our development and regulatory strategy, based on the performance of the drug. At the end of 1998, we performed an interim analysis of the results of this trial. The purpose of the analysis was to support internal planning. Consistent with our original strategy and FDA requirements, we will not make the results of that analysis public. We are conducting additional studies of ISIS 2302 in Crohn's disease to determine whether shorter courses of treatment or subcutaneous dosing can be effective. These studies should be completed in 1999 and, if positive, may support easier, more convenient dosing. The program may be expanded to include additional pivotal studies based on analysis of the data from ongoing trials.

We recently completed the analysis of the Phase II, 43 patient 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.

The Phase II study in kidney transplant rejection is also proceeding at a pace mandated by the regulatory authorities, as they carefully monitor clinical studies in this patient population. We anticipate that this study will be completed in mid-1999. We will make the data available after the study is completed.

We are also pursuing development of ISIS 2302 as a topical treatment for psoriasis, as an enema formulation for treatment of ulcerative colitis, and as an aerosol formulation for treatment of asthma. Our goal is to initiate clinical trials in as many of these indications as resources permit in the near term. Boehringer Ingelheim and we will determine the timing of these initiatives.

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 (LOGO)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-(LOGO) 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.

The Phase I studies included 56 patients with various types of cancer that had not responded to standard treatment. In one study, 36 patients received the drug via a 2-hour infusion 3 times per week for 3 weeks, with redosing every 4 weeks. In a second study, 20 patients received the drug via a 21-day continuous infusion for 3 weeks repeated every 4 weeks. The primary endpoint of the Phase I trials was safety, and all patients were assessed for antitumor effects. 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. In the short infusion study, 1 patient with lymphoma experienced a partial response (defined as a greater than 50% reduction in measurable disease) that has continued for more than 16 months from the start of therapy. Another patient with lymphoma has had a partial response lasting more than 8 months, and 1 patient with non-small cell lung cancer has experienced disease stabilization for 8 months. In the continuous infusion study, 3 of 4 patients with ovarian cancer showed a decrease in disease. One patient, whose abdominal mass had doubled in size in the month prior to entering the study, experienced a partial response for over 11 months before progressing. One patient experienced a 40% decrease in CA-125, an ovarian tumor marker, for over 5 months and 1 patient experienced a 75% decrease in CA-125 for more than 7 months.

We initiated Phase II clinical trials in the third quarter of 1997. In the Phase II trials, we are evaluating ISIS 3521 in both single-agent and combination studies in patients with a variety of solid tumors, including ovarian, prostate, breast, brain, colon and lung cancers, and melanomas. We have also been conducting trials of ISIS 3521 in combination with chemotherapy agents commonly used against a variety of tumors. We anticipate that the Phase II program and the Phase I combination trials will be completed in the second half of 1999, at which point, we and our partner, Novartis, will determine next development steps.

We are developing ISIS 3521 as part of our antisense research and development collaboration with Novartis. Isis also has additional PKC-(LOGO)inhibitors in preclinical development which incorporate second

generation chemistry and which have the potential for increased safety and more convenient dosing, possibly including oral delivery. Isis also has lead compounds that inhibit two isotypes of the PKC family, including PKC-(LOGO), believed to be involved in cancer and other diseases.

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. Studies of ISIS 5132 in cell culture and in nude mouse xenograft models using human tumor cells show that ISIS 5132 inhibits expression of the target C-raf gene.

In Phase I clinical trials, ISIS 5132 was very well-tolerated. Several patients in this trial experienced disease stabilization. In the 2-hour infusion study, 1 patient with colon cancer experienced a decrease in CEA, a colon cancer marker, with no growth in tumor for approximately 7 months. Another patient with kidney cancer experienced disease stabilization for more than 9 months and continues to be on study. In the continuous infusion study, 1 patient with pancreatic cancer experienced disease stabilization for 7 months and continues on study, 1 patient with kidney cancer experienced disease stabilization for 9 months, and 1 patient with ovarian cancer had a 97% drop in CA-125 after 6 months.

We initiated Phase II clinical trials of ISIS 5132 in the fourth quarter of 1997. In the Phase II trials, we are evaluating ISIS 5132 as a single-agent in studies of patients with a variety of solid tumors, including prostate, breast, ovarian, pancreatic, colon and both small-cell and non-small cell lung cancers. We have also been conducting trials of ISIS 5132 in combination with chemotherapy agents commonly used against a variety of tumors. We anticipate that the Phase II program and the Phase I combination trials will be completed in the second half of 1999, at which point, we and Novartis will determine next development steps.

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 the fall of 1997, we initiated Phase I clinical trials of ISIS 2503. This trial involved patients with a variety of solid tumors that had not responded to standard cancer therapies. In Phase I clinical trials ISIS 2503 has been well-tolerated and has displayed an excellent safety profile. The Phase I trials are nearly complete. Once completed, data from these studies will be analyzed and presented publicly in an appropriate scientific meeting.

Phase II trials of ISIS 2503 will begin in early 1999 and should take about one year to complete. The Phase II program will include four different tumor types and treat about 120 patients. Tumor types selected are those in which the ras proteins are known to contribute to tumor development and maintenance. We are particularly interested in testing ISIS 2503 in gastrointestinal cancers. We will initiate clinical trials of ISIS 2503 in combination with conventional chemotherapy in the first half of 1999.

RESEARCH PROGRAMS

We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drug candidates. The goal of our target-based research programs is to identify antisense and Ibis 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 both on cell adhesion molecules in connection with our collaboration with Boehringer Ingelheim and on identifying broad-spectrum antibacterial agents with a focus on important drug-resistant infections.

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. Through these programs, we can efficiently explore numerous disease targets and

identify the best lead compounds to advance into preclinical development. We are currently pursuing antisense and Ibis 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.

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. At Novartis' expense, we are conducting clinical development of ISIS 3521 and ISIS 5132. Novartis will pay us royalties on the sales of any licensed compound. We have the right to commercially manufacture ISIS 3521 and ISIS 5132 for additional royalties. See "Products Under Development -- Cancer -- ISIS 3521; ISIS 5132." As of February 26, 1999, Novartis owned approximately 9% of our outstanding Common Stock.

Boehringer Ingelheim

In July 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. We contribute our expertise in antisense and combinatorial drug discovery and Boehringer Ingelheim contributes its ongoing program in cell adhesion biology and small molecule library screening capabilities. Both companies provide ongoing funding for the combined research and development program. Either party may terminate the funding requirements under the collaboration agreement if, at the end of five years, there are no compounds being developed or commercialized jointly.

In addition to funding one-half of the collaboration's research and development, Boehringer Ingelheim will make additional investments in us as certain development milestones are met. Boehringer Ingelheim has already paid us a milestone payment of $10 million for the completion of the first Phase II clinical trial of ISIS 2302 in Crohn's disease. It also provides us with a $40 million line of credit, which is available under certain circumstances. As of December 31, 1998, outstanding borrowings under this line of credit totaled $22.6 million.

The partnership includes development of ISIS 2302, an antisense inhibitor of ICAM-1, and multiple other preclinical and research compounds targeting other adhesion molecules. We and Boehringer Ingelheim will split the operating profits associated with all future products of the partnership. If a partner chooses not to continue to fund its share of the development expenses for a compound, it will receive a certain amount of royalties on any future sales of such compounds rather than a split of operating profits. Boehringer Ingelheim will market the first two drugs resulting from the collaboration. Both companies will agree on commercialization responsibilities for any products to follow.

ISIS 2302 is in a pivotal quality trial for Crohn's disease and clinical trials of various stages for other indications. This compound is being developed by an Isis-led project team as part of the collaboration. See "Products Under Development -- Inflammatory Diseases."

As of February 26, 1999, Boehringer Ingelheim owned approximately 9% of our outstanding Common Stock.

CIBA Vision

In July 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, 1998, we have received a total of $12.5 million of the 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. CIBA Vision also has the option to acquire the exclusive license to market and distribute our second generation antisense compound to treat CMV retinitis, ISIS 13312, which is currently in preclinical development. See "Products Under Development -- Cytomegalovirus (CMV) Retinitis."

Zeneca Pharmaceuticals

In December 1998, we established a new antisense collaboration with Zeneca Pharmaceuticals to discover, develop and commercialize novel antisense drugs targeting specific genes associated with cancer. In this collaboration, we will create antisense candidates and work together with Zeneca to optimize them. Zeneca will develop drugs arising out of the collaboration. Zeneca 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 December 1998, Zeneca paid $2 million in technology access fees. While the initial focus of this collaboration is on a limited number of cancer targets, we can, with Zeneca, 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 & Co.

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 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, we received a total of $3.9 million from Merck under the terms of this agreement.

Abbott Laboratories, Inc.

In December 1998, we entered into an Antisense Target Validation, or ATV, collaboration with Abbott Laboratories, Inc. The collaboration will utilize our ATV 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. In 1998, we received an initial payment of $250,000.

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 March 1998, we established an antisense oligonucleotide manufacturing collaboration with Zeneca 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. Under the terms of the five-year agreement, Zeneca LSM will supplement our primary manufacturing facility in producing antisense oligonucleotides for use in clinical trials. The agreement specifies that we will have Zeneca LSM manufacture a certain portion of the drug supplies required for its clinical trials. We are not required to make any capital investment to create this manufacturing capability.

PATENTS AND PROPRIETARY RIGHTS

Our success will depend, in part, on our ability to obtain patent protection for our products in the United States and other countries. We file applications, as appropriate, for patents covering our products and processes. As of January 31, 1999, we have been issued more than 200 patents in the United States and foreign countries, have received more than 35 U.S. notices of allowance and have filed more than 400 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 protect our rights to the building blocks of our compounds;

- Composition of matter claims to messenger RNA target sequences, which protect our rights to the genetic sequences that our compounds target;

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

- Method claims for the manufacture of oligonucleotides, which protect our new, improved or more cost effective ways to manufacture oligonucleotides.

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. We believe that we are in compliance in all material respects with applicable laws and regulations.

COMPETITION

For many of their applications, including CMV retinitis, antisense based drugs 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 equiped 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 26, 1999, we employed 346 individuals, of whom 143 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 March 15, 1999 are as follows:

STANLEY T. CROOKE, M.D., PH.D. . . . 53
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 Megabios Corp., SIBIA Neurosciences, Inc., and Idun Pharmaceuticals, Inc. all biotechnology companies, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

B. LYNNE PARSHALL . . . 43
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. . . . 47
Executive Vice President

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

C. FRANK BENNETT, PH.D. . . . 42
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. . . . 44
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 . . . 52
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 its optimum dosage, 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.

While limited trials of our products have to date produced favorable results, significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products. 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, 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 to our partner CIBA Vision in 1998, earning product revenue of $560,000.

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.

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, 1998, our accumulated losses were approximately $197 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential 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 thereon, will be adequate to satisfy our capital needs until at least the end of 2000.

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;

- 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 may 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 Zeneca Life Science Molecules of Manchester, England pursuant to which Zeneca LSM will supply a portion of our requirements of drugs for clinical trials. As of the date of this prospectus, we have not received any supply of drugs under this arrangement, and we cannot guarantee that Zeneca 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 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.

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. Such disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and 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. Although we might under these circumstances attempt to obtain a license to such intellectual property, we may not be able to do so 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. Recently, Dr. Daniel Kisner, our President and Chief Operating Officer and director resigned all positions to assume the position of Chief Executive Officer of Caliper Technologies, a privately held company. Dr. Kisner's resignation is not expected to have a material adverse effect on our business. It is also critical to our success to recruit and retain qualified scientific personnel to perform research and development work. Although we believe we will be successful in attracting and keeping skilled and experienced scientific personnel, we may not be able to do so 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 $7 to $16. 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 our outstanding common stock. The classified board, stockholder vote requirements and other charter provisions protect us in two ways. First, 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. Second, 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 132,000 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, 1998, secure approximately $8.6 million in indebtedness of the Company. Two of the buildings are leased. 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 1999.

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 (Nasdaq symbol "ISIP") is traded publicly through the Nasdaq National Market. 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
1997		
First Quarter	$19.88	$15.00
Second Quarter	$17.38	$12.88
Third Quarter	$18.63	$12.75
Fourth Quarter	$18.38	$11.00
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

As of January 31, 1999, there were approximately 1,427 stockholders of record of the 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."

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

	YEARS ENDED DECEMBER 31,				
	1998	1997	1996	1995	1994
STATEMENT OF OPERATIONS DATA:					
Research and development revenues	$ 38,611	$ 32,722	$ 22,663	$ 12,966	$ 10,088
Research and development expenses	62,200	55,940	45,653	33,175	26,468
Net loss	(42,983)	(31,066)	(26,521)	(23,712)	(18,181)
Basic and diluted net loss per share	(1.60)	(1.17)	(1.04)	(1.10)	(0.93)
Shares used in computing basic and diluted net loss per share	26,873	26,456	25,585	21,514	19,542

	DECEMBER 31,				
	1998	1997	1996	1995	1994
BALANCE SHEET DATA:					
Cash, cash equivalents and short-term investments	$ 58,848	$ 86,786	$ 77,624	$ 77,407	$ 43,440
Working capital	40,651	62,573	56,300	60,040	33,679
Total assets	96,074	117,881	101,305	99,569	66,643
Long-term debt and capital lease obligations, less current portion	77,724	56,452	19,864	4,714	9,295
Accumulated deficit	(197,116)	(154,133)	(123,067)	(96,546)	(72,834)
Stockholders' equity	(4,186)	34,852	58,385	75,850	46,019

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

Since its inception in January 1989, almost all of our resources have been devoted to its 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, 1998 and December 31, 1997

Our revenue from collaborative research and development agreements was $38.6 million for the year ended December 31, 1998 compared with $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 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 rose 11% to $62.2 million in 1998 from $55.9 million in 1997. The increase in research and development expenses occurred because compounds in preclinical and clinical development are continuing to advance into more expensive stages of development. We expect that research and development expenses will continue to increase as compounds continue to advance in clinical development.

Operating expenses in 1998 included $5.2 million for acquired patents. Isis purchased the Gilead Sciences, Inc. patent estate, which includes patents and patent applications covering proprietary antisense chemistry and drug delivery systems. We acquired the Gilead patents to enhance our dominant proprietary position in antisense technology. We also believe that the acquisition of the Gilead patents may reduce the risk of possible future patent infringement claims. Effort will be required by our scientists to determine if the acquired patents can be developed into potentially viable products. The scope of the effort to be invested by our scientists is within the bounds of our existing research and development budgets. As our 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, we wrote off the acquired patents in 1998. No similar expenses were incurred in 1997.

General and administrative expenses were $9.5 million for 1998 compared with $8.1 million in 1997. This increase is primarily because of expanded business development, investor relations activities and support of our increasing research and development efforts. We expect that general and administrative expenses will continue to increase in the future to support our growing research and development activities.

Interest expense increased to $9.4 million in 1998 compared with $3.6 million in 1997. This increase in interest expense is due to borrowing $25 million in a private debt financing completed in the fourth quarter of 1997 with an additional $15 million follow-on private debt financing in the second quarter of 1998. Under the terms of these financing arrangements, payment of both principal and interest is deferred for the first five years. Therefore, of the $9.4 million interest expense in 1998, $6.1 million was accrued under the long-term debt agreements and will not require current cash payment.

Our net loss for 1998 was $43.0 million, or $1.60 per share, compared to $31.1 million, or $1.17 per share, for 1997. We expect that operating losses will increase for several more years as research and development activities grow. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

At December 31, 1998, our net operating loss carryforward for federal income tax purposes was approximately $193.5 million. The net operating loss and research credit carryforwards make up the majority of our deferred tax assets. We will only be able to use the net operating loss and research credits, and realize the benefit of these deferred tax assets, if we become profitable. We have fully reserved all of our deferred tax assets as their realization is uncertain. Our research credit carryforward for federal income tax purposes was approximately $8.4 million. 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.

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

Years Ended December 31, 1997, and December 31, 1996

Our revenue from collaborative research and development agreements was $32.7 in 1997 and $22.7 million in 1996, an increase of 44%. The receipt of a $5 million pre-commercial fee from CIBA Vision together with $4 million in milestone payments from Novartis in addition to ongoing revenue from research and development collaborations caused this revenue increase.

Research and development expenses amounted to $55.9 million in 1997 and $45.7 million in 1996. This increase in research and development expenses resulted from Isis' growing preclinical and clinical development activities.

General and administrative expenses were $8.1 million in 1997 compared with $6.2 million in 1996. This increase was due to expanded business development and investor relations activities and support of our increasing research and development efforts.

Our net loss was $31.1 million, or $1.17 per share, in 1997 and $26.5 million, or $1.04 per share, in 1996.

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, 1998, we have earned approximately $145 million in revenue from contract research and development. We have also raised net proceeds of approximately $185 million from the sale of equity securities since Isis was founded. We have borrowed approximately $60 million under long-term debt arrangements to finance a portion of our operations.

As of December 31, 1998, we had cash, cash equivalents and short-term investments of $58.8 million and working capital of $40.7 million. In comparison, we had cash, cash equivalents and short-term investments of $86.8 million and working capital of $62.6 million as of December 31, 1997. This decrease in cash and short-term investments resulted from the funding of operating losses, investments in capital equipment and building improvements and principal payments on debt and capital lease obligations. This decrease was offset in part by the receipt of $15 million from a private debt financing and $12.5 million in milestone payments and licensing fees from CIBA Vision and CpG ImmunoPharmaceuticals, Inc.

The agreement with Boehringer Ingelheim provides us with a $40 million line of credit. This line of credit is to be used to support the collaboration cell adhesion programs. Restrictions on the availability of the line of credit are based on the anticipated collaboration costs, the amount of funds available to us, and our average stock price over specified periods. As of December 31, 1998 the line of credit was not available. We expect that the line of credit will be available again in mid-1999. As of December 31, 1998, the outstanding balance under this line of credit was $22.6 million. See Note 3 to the Financial Statements, "Long-term obligations and commitments."

In October 1997, we borrowed $25 million in a private transaction. The loan must be repaid on November 1, 2007, and bears interest at 14% per annum. No payments of either principal or interest are required during the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan. No principal payments are required until November 1, 2007. In conjunction with this transaction, we issued warrants to purchase 500,000 shares of common stock at a price of $25 per share. On May 1, 1998, we completed a follow-on $15 million private debt financing. This financing was a follow-on to our $25 million private debt financing in October 1997 and bears the same terms and conditions. In conjunction with this follow-on transaction, we issued warrants to purchase 300,000 shares of common stock at a price of $25 per share. The warrants issued in connection with both of these financings expire on November 1, 2004. The warrants have been valued at 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, 1998 was $41,321,000. See Note 3 to the Financial Statements, "Long-term obligations and commitments".

As of December 31, 1998, our long-term obligations totaled $81.3 million compared to $58.7 million at December 31, 1997. This increase was due to the $15 million follow-on debt financing together with the accrual of interest on the ten-year notes 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 growing business. We will continue to use lease lines as long as the terms continue to remain commercially attractive. We believe that our existing cash, cash equivalents and short-term investments, combined with interest income and contract revenue will be sufficient to meet our anticipated requirements at least until the end of 2000.

YEAR 2000 COMPUTER ISSUES

Until recently many computer programs were written to store only two digits of date-related information. Thus the programs were unable to distinguish between the year 1900 and the year 2000. As a result, many computer experts have significant concerns regarding how those programs will function after December 31, 1999. This is frequently referred to as the "Year 2000 Problem." Because Isis was founded in 1989, our computer systems and equipment are relatively new and generally not subject to the date and time issues that create the Year 2000 problems.

A team of Isis employees is conducting our Year 2000 initiative. The team's activities are designed to ensure that there is no adverse effect on our core business operations and that transactions with customers, suppliers, corporate partners and financial institutions are fully supported. Our Year 2000 plan includes the following phases: inventorying critical business systems and vendors, assessment of the probability of Year 2000 non-compliance, remediation activities including repairing or replacing identified systems, testing, and developing contingency plans.

An inventory of all computer equipment, operating systems and applications including other equipment that uses embedded microprocessors has been completed. Compliance assessment has been completed for all critical or important systems and equipment. Remediation activities have been completed for all but five systems or pieces of equipment. We estimate that all required remediation and validation will be completed by the third quarter of 1999. Testing of our critical and important systems and applications is ongoing and is scheduled to be completed by the third quarter of 1999. Contingency planning will begin in the second quarter of 1999. Based on the work completed to date, we believe that with the completed remediation work, the Year 2000 issue will not pose significant operational problems for our computer systems and equipment.

We have also requested information from our significant suppliers, corporate partners and financial institutions to ensure that those parties are addressing Year 2000 issues where their systems could impact our operations. We are assessing the extent to which our operations are vulnerable should those organizations fail to properly modify their computer systems. The failure of systems maintained by our vendors, corporate partners or financial institutions could affect our ability to process transactions, conduct research and development projects, manufacture products, or engage in other normal business activities. We have received responses from all but one of the critical or important third parties and are in the process of evaluating those responses to identify areas of exposure. We are also in the process of identifying alternate sources for products or services in the event that any of our present primary or secondary vendors are not successful in resolving their Year 2000 issues. We will continue to monitor the progress of critical and important third parties throughout 1999 to ascertain that they achieve their Year 2000 objectives.

Our most likely exposure to Year 2000 problems is related to our high dependence on commercial utilities such as water and power. If the providers of these utilities are not able to maintain service due to Year 2000 noncompliance it could result in temporarily halting research and development activities until the service is restored or until suitable alternate facilities in a different geographic area could be obtained. It is not

possible to precisely estimate the length of delays in research and development projects in those circumstances, but it could range from three to six months.

While we believe our planning and preparations will be adequate to address our internal Year 2000 concerns, we cannot guarantee that the systems of other companies, on which our systems and operations rely, will be converted on a timely basis and will not have a material effect on us. The total cost of the Year 2000 risk assessment and remediation is funded through operating cash flows, and we are expensing these costs as they are incurred. Based on information obtained to date, the cost of identifying and remediating exposures to the Year 2000 Problem is not expected to be material to our results of operations or financial position. The estimated total cost of our Year 2000 assessment and remediation is not expected to exceed $500,000.

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 12, 1999 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 1999 Annual Meeting of stockholders to be held on May 21, 1999.

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 35 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 34.

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 (the "Plan").(5)
10.3	--	Revised form of Incentive Stock Option Agreement under the Plan.(1)
10.4	--	Revised form of Supplemental Stock Option Agreement under the Plan.(1)
10.5	--	Form of Incentive Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule.(2)
10.6	--	Form of Supplemental Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule.(2)
10.7	--	Registrant's 1992 Non-employee Directors Stock Option Plan, as amended.(1)
10.8	--	Revised form of Supplemental Stock Option Agreement under Registrant's 1992 Non-employee Directors' Stock Option Plan, as amended.(4)
10.9	--	Registrant's Employee Stock Purchase Plan.(3)

- ---

(1) 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.

(2) 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.

(3) Filed as an exhibit to the Registrant's Registration Statement on Form S-8 (No. 33-42970) 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

There were no reports on Form 8-K filed by the Registrant during the fourth quarter of the fiscal year ended December 31, 1998.

(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/A to be signed on its behalf by the undersigned, thereunto duly authorized on the 14th day of June, 1999.

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)	June 14, 1999
* B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	June 14, 1999
* Burkhard Blank	Director	June 14, 1999
* Christopher F. O. Gabrieli	Director	June 14, 1999
* Alan C. Mendelson	Director	June 14, 1999
* William R. Miller	Director	June 14, 1999

SIGNATURES	TITLE	DATE
*	Director	June 14, 1999
Mark B. Skaletsky		
*	Director	June 14, 1999
Larry Soll		
*	Director	June 14, 1999
Joseph H. Wender		

By: /s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Attorney in Fact

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 Plan.(8)
10.4	Revised form of Supplemental Stock Option Agreement under the Plan.(8)
10.5	Form of Incentive Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule.(4)
10.6	Form of Supplemental Stock Option Agreement 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	Registrant's Employee Stock Purchase Plan.(2)
10.10	Form of Employee Assignment of Patent Rights.(1)
10.11	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)
10.12	License Agreement between the Registrant and the PNA Group dated as of January 29, 1992 (with certain confidential information deleted).(3)
10.13	Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(5)
10.14	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(6)
10.15	Agreement between Registrant and CIBA Vision Corporation dated July 10, 1997 (with certain confidential information deleted).(9)
10.16	Amendment No. 2 to the Agreement between the Company and CIBA Vision Corporation, dated September 14, 1998 (with certain confidential information deleted).(12)
10.17	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)
10.18	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)

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
10.19	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)
10.20	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)
10.21	Asset Purchase Agreement between Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(10)
10.22	Research Collaboration and License Agreement between Merck & Co., Inc. and Isis Pharmaceuticals, Inc. dated June 1, 1998 (with certain confidential information deleted).(11)
10.23	Research and Development Agreement between Isis Pharmaceuticals, Inc. and Zeneca Limited, dated December 18, 1998 (with certain confidential information deleted).
10.24	Patent Rights Purchase Agreement between Isis Pharmaceuticals, Inc. and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(13)
23.1	Consent of Ernst & Young LLP.(14)
24.1	Power of Attorney. Reference is made to page 29.
27.1	Financial Data Schedule.(13)

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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.

(14) Filed as an exhibit to the Registrant's Annual Report on Form 10-K (Amendment No.1) for the year ended December 31, 1998.

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, 1998 and 1997, and the related statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 1998. 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 generally accepted auditing standards. 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, 1998 and 1997, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 1998, in conformity with generally accepted accounting principles.

ERNST & YOUNG LLP

San Diego, California
January 30, 1999

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

	DECEMBER 31,	
	1998	1997
Current assets:		
Cash and cash equivalents	$ 27,618	$ 38,102
Short-term investments	31,230	48,684
Contracts receivable	3,466	289
Prepaids and other current assets	873	2,075
Total current assets	63,187	89,150
Property, plant and equipment, net	21,542	18,785
Patent costs, net	9,113	7,485
Deposits and other assets	2,232	2,461
	$ 96,074	$117,881

LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)

Current liabilities:		
Accounts payable	$ 2,977	$ 2,843
Accrued payroll and related expenses	3,088	2,242
Accrued liabilities	2,714	4,347
Deferred contract revenues	10,176	14,893
Current portion of long-term obligations	3,581	2,252
Total current liabilities	22,536	26,577
Long-term obligations, less current portion	77,724	56,452
Commitments (See Note 3)		
Stockholders' equity (deficit):		
Common stock, $.001 par value; 50,000,000 shares authorized, 27,053,000 shares and 26,655,000 shares issued and outstanding at December 31, 1998 and 1997, respectively	27	27
Additional paid-in capital	192,737	188,793
Accumulated other comprehensive income	166	165
Accumulated deficit	(197,116)	(154,133)
Total stockholders' equity (deficit)	(4,186)	34,852
	$ 96,074	$117,881

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

	YEAR ENDED DECEMBER 31,		
	1998	1997	1996
Revenues:			
Research and development revenues under collaborative agreements	$ 38,611	$ 32,722	$ 22,663
Product revenues	560	--	--
	39,171	32,722	22,663
Expenses:			
Research and development	62,200	55,940	45,653
Write-off of acquired patents	5,238	--	--
General and administrative	9,511	8,078	6,246
Total operating expenses	76,949	64,018	51,899
Loss from operations	(37,778)	(31,296)	(29,236)
Interest income	4,150	3,815	3,921
Interest expense	9,355	3,585	1,206
Net loss	$(42,983)	$(31,066)	$(26,521)
Basic and diluted net loss per share	$ (1.60)	$ (1.17)	$ (1.04)
Shares used in computing basic and diluted net loss per share	26,873	26,456	25,585

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

DESCRIPTION	COMMON STOCK SHARES	COMMON STOCK AMOUNT	ADDITIONAL PAID IN CAPITAL	ACCUMULATED OTHER COMPREHENSIVE INCOME	ACCUMULATED DEFICIT	TOTAL STOCKHOLDERS' EQUITY
Balance at December 31, 1995.....	25,249	$25	$172,253	$118	$ (96,546)	$ 75,850
Comprehensive Income.....	--	--	--	--		
Net loss.....	--	--	--	--	(26,521)	(26,521)
Changes in unrealized gains and (losses), net of income taxes.....	--	--	--	60	--	60
Comprehensive Income.....						(26,461)
Options exercised and employee stock purchase plan.....	543	1	3,164	--	--	3,165
Issuances of common stock net of repurchases and offering costs.....	409	--	5,822	--	--	5,822
Compensation relating to the granting of options.....	--	--	9	--	--	9
Balance at December 31, 1996.....	26,201	26	181,248	178	(123,067)	58,385
Comprehensive Income.....	--	--	--	--		
Net loss.....	--	--	--	--	(31,066)	(31,066)
- --						
Change in unrealized gains and (losses),net of income taxes...	--	--	--	(13)	--	(13)
Comprehensive Income.....						(31,079)
Options exercised and employee stock purchase plan.....	454	1	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.....	26,655	27	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.....						(42,982)
Options exercised and employee stock purchase plan.....	398	--	2,298	--	--	2,298
Issuances of warrants to purchase common stock.....	--	--	1,646	--	--	1,646
Balance at December 31, 1998.....	27,053	$27	$192,737	$166	$(197,116)	$ (4,186)

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	YEAR ENDED DECEMBER 31,		
	1998	1997	1996
Operating activities:			
Net loss	$(42,983)	$(31,066)	$(26,521)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	4,258	3,178	2,633
Deferred interest on long term debt	6,112	654	--
Write-off of acquired patents	5,238	--	--
Compensation related to grant of options	--	459	9
Changes in operating assets and liabilities:			
Contracts receivable	(3,177)	(289)	--
Prepaids and other current assets	1,202	(343)	(94)
Accounts payable	134	481	1,365
Accrued payroll and related expenses	846	753	240
Accrued liabilities	(1,633)	1,584	(75)
Deferred contract revenues	(4,717)	4,689	1,291
Net cash used in operating activities	(34,720)	(19,900)	(21,152)
Investing activities:			
Short-term investments	17,454	(8,142)	(9,598)
Unrealized gain on investments	1	(13)	60
Property, plant and equipment	(4,434)	(3,454)	(862)
Patent costs	(3,882)	(1,455)	(1,439)
Deposits and other assets	(30)	(2,098)	568
Net cash provided by (used in) investing activities	9,109	(15,162)	(11,271)
Financing activities:			
Net proceeds from issuance of equity	3,944	7,087	8,987
Proceeds from long-term borrowing	13,354	32,666	16,200
Principal payments on debt and capital lease obligations	(2,171)	(3,671)	(2,145)
Net cash provided from financing activities	15,127	36,082	23,042
Net increase (decrease) in cash and cash equivalents	(10,484)	1,020	(9,381)
Cash and cash equivalents at beginning of year	38,102	37,082	46,463
Cash and cash equivalents at end of year	$ 27,618	$ 38,102	$ 37,082
Supplemental disclosures of cash flow information:			
Interest paid	$ 3,191	$ 2,644	$ 1,150
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt and capital lease obligations for acquisitions of property, plant and equipment	$ 2,068	$ 2,953	$ 2,325
Additions to debt for patent acquisitions	$ 3,238	$ --	$ --

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1998

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 -- In 1997, the Financial Accounting Standards Board issued Statement No. 128, "Earnings Per Share." Statement No. 128 replaced the calculation of primary and fully diluted earnings per share with basic and diluted earnings per share. Basic earnings per share 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. All net losses per share have been presented to conform to Statement No. 128 requirements.

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, 1998, 1997 and 1996, costs and expenses of approximately $35,000,000, $31,000,000, and $29,000,000 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.

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, 1998, and has classified all of its investments as available-for-sale. This category includes all securities which Isis does not have the positive intent and ability to hold to maturity. The measurement basis for available-for-sale securities is fair market value. Unrealized gains and losses, net of the related tax effect, are included in accumulated other comprehensive income, a separate component of stockholders' equity. 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,	
	1998	1997
Land	$ 1,163	$ 1,163
Buildings and improvements	16,084	13,607
Equipment	25,324	21,599
Furniture and fixtures	1,227	927
	43,798	37,296
Less accumulated depreciation	(22,256)	(18,511)
	$ 21,542	$ 18,785

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 is 8.2 years. Accumulated amortization was $493,000 at December 31, 1998 and $240,000 at December 31, 1997.

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 market value or discounted cash flow 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 -- Isis adopted Statement of Financial Accounting Standards (FAS) 130, "Reporting Comprehensive Income", at December 31, 1998. Under FAS 130, Isis is required to display comprehensive income and its components as part of Isis' full set of financial statements. The measurement and presentation of net income did not change. Comprehensive income is comprised of net income and certain changes in equity that are excluded from net income. 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. Comprehensive income for the years ended December 31, 1998, 1997 and 1996 have been reflected in the Consolidated Statement of Stockholders' Equity.

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, 1998, 79% of the debt securities held by Isis had a contractual maturity of one year or less, and the remaining 21% of the portfolio was due within 2 years.

The following is a summary of available-for-sale securities:

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS	ESTIMATED FAIR VALUE
		(IN THOUSANDS)	
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
DECEMBER 31, 1997			
U.S. Treasury securities and obligations of U.S. Government agencies	$32,980	$105	$33,085
U.S. corporate debt securities	15,539	60	15,599
Total debt securities	$48,519	$165	$48,684

3. LONG-TERM OBLIGATIONS AND COMMITMENTS

Isis obtained $25,060,000 in private debt financing during 1997 and an additional $15,000,000 in 1998. 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 500,000 common shares in 1997 and 300,000 shares in 1998. 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%. The warrants were valued at $3,780,000 and $1,646,000 respectively, and were 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, 1998 was $41,321,000. The fair value of this debt at December 31, 1998 approximated $45,000,000. 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, 1998 was $3,451,000. 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, 1998 was $5,150,000. As of December 31, 1998, 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 are being 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 is 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, 1998 was $22,576,000, which approximated fair value.

In December 1998, Isis purchased from Gilead Sciences, Inc. ("Gilead"), 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 the next three years. Isis made the initial $2,000,000 payment in December 1998. 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, 1998 was $3,238,000, 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, 1998 are as follows (in thousands):

	OPERATING LEASES	CAPITAL LEASES	CONTRACT OBLIGATIONS	LONG-TERM DEBT
1999	$1,150	$ 2,426	$1,000	$ 3,388
2000	859	1,797	1,000	3,321
2001	856	1,610	2,000	3,253
2002	797	645		8,574
2003	778	9		28,955
Thereafter	2,238	1		128,156
Total minimum payments	$6,678	$ 6,488	$4,000	$ 175,647
Less amount representing interest		(919)	(762)	(103,149)
Present value of future minimum payments		5,569	3,238	72,498
Less current portion		(1,923)	(909)	(749)
Total		$ 3,646	$2,329	$ 71,749

Rent expense for the years ended December 31, 1998, 1997, and 1996 was $1,328,000, $1,030,000 and $520,000, respectively. Cost of equipment under capital leases at December 31, 1998 and 1997 was $17,227,000 and $14,133,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 1998 and 1997 was $13,266,000 and $11,177,000, respectively.

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, 1998, a total of 4,347,000 shares were exercisable, and 1,903,000 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, 1998, 139,000 shares issued under this plan were exercisable and 58,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 1998 and 1997 (in thousands, except per share data):

	NUMBER OF SHARES	PRICE PER SHARE	WEIGHTED AVG. PRICE/SHARE
Outstanding at December 31, 1995.....	5,446	$ .14 to $19.75	
Granted.....	1,337	11.38 to 20.00	
Exercised.....	(468)	.14 to 17.88	
Terminated.....	(222)	4.00 to 18.63	
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

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 12/31/98	WEIGHTED AVERAGE REMAINING CONTRACTUAL LIFE	WEIGHTED AVERAGE EXERCISE PRICE	NUMBER EXERCISABLE AS OF 12/31/98	WEIGHTED AVERAGE EXERCISE PRICE
$ 0.14 - $ 4.00..	900	4.51	$ 3.32	649	$ 3.09
$ 4.13 - $ 6.38..	825	4.71	$ 5.68	772	$ 5.70
$ 6.46 - $ 7.75..	896	4.90	$ 6.88	864	$ 6.87
$ 7.88 - $11.88..	1,052	5.68	$ 9.91	769	$ 9.66
$12.00 - $12.31..	851	8.64	$12.29	88	$12.22
$12.31 - $13.13..	891	7.02	$13.02	621	$13.03
$13.18 - $16.19..	831	7.82	$14.54	333	$14.61
$16.25 - $19.88..	740	7.69	$17.99	390	$17.94
$ 0.14 - $19.88..	6,986	6.46	$10.27	4,486	$ 9.10

Employee Stock Purchase Plan -- In 1991, the Board of Directors adopted the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance thereunder. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the

offer or the end of

each six-month purchase period. During 1998, 78,000 shares were issued to employees at prices ranging from $10.47 to $10.73 per share. In 1997, 58,000 shares were issued at prices ranging from $10.73 to $15.30 per share. At December 31, 1998, 141,000 shares were available for purchase under this plan.

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

	1998	1997	1996
Net loss -- as reported	$(42,983)	$(31,066)	$(26,521)
Net loss -- pro forma	(49,761)	(38,004)	(32,200)
Basic net loss per share -- as reported	$ (1.60)	$ (1.17)	$ (1.04)
Basic net loss per share -- pro forma	(1.85)	(1.44)	(1.26)

The fair value of each option grant is estimated on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions for 1996, 1997 and 1998: expected life of 1 year from vesting date for regular employees, 2 years from vesting date for Directors and Vice Presidents, and 4 years from vesting date for Executive Officers; expected dividend yield of zero percent and expected volatility of 60 percent. The risk-free interest rate was based on the Treasury Bill rate at the end of each year during 1996, 1997 and 1998. The weighted average risk free interest rates for 1996, 1997 and 1998 were 6.1%, 5.7%, and 4.6%, 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 $7.20 for 1996, $8.50 for 1997 and $5.98 for 1998.

Warrants -- In 1993, Isis issued Class A warrants in connection with a strategic alliance with PerSeptive Biosystems, Inc. As of December 31, 1998, 448,001 of the warrants remain outstanding at an exercise price of $7.75 per share. The warrants expire March 15, 1999.

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, 1998, all of the warrants remain outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3.

As of December 31, 1998, total common shares reserved for future issuance was 10,429,000.

5. INCOME TAXES

Significant components of Isis' deferred tax assets as of December 31, 1998 and 1997 are shown below. Valuation allowances of $90,931,000 and $71,400,000 have been recognized for 1998 and 1997, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	1998	1997
Deferred tax assets:		
Capitalized research expense	$ 8,320,000	$ 7,741,000
Net operating loss carryforwards	69,661,000	57,959,000
Research and development credits	10,849,000	7,258,000
Other, net	5,314,000	889,000
Total deferred tax assets	94,144,000	73,847,000
Deferred tax liabilities:		
Patent expense	(3,213,000)	(2,447,000)
Total deferred tax liabilities	(3,213,000)	(2,447,000)
Total net deferred tax assets	90,931,000	71,400,000
Valuation allowance for deferred tax assets	(90,931,000)	(71,400,000)
Net deferred tax assets	$ 0	$ 0

At December 31, 1998, approximately $3,627,000 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, 1998, Isis had federal and California tax net operating loss carryforwards of approximately $193,526,000 and $33,507,000, respectively. Isis also had federal and California research credit carryforwards of approximately $8,402,000 and $3,765,000, 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 $3,100,000 of the California tax loss carryforward expired during 1998 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 1999, 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 4 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 includes research to discover additional therapeutic compounds. Under the terms of the expanded collaboration, Novartis is funding the development of both ISIS 3521 and ISIS 5132. Isis receives certain milestone payments from Novartis as these compounds and subsequent compounds arising out of the expanded research program progress through development. Novartis will market these compounds worldwide and will pay Isis a royalty based on sales. Included in the statement of operations for

the years ended December 31, 1998, 1997 and 1996 are contract revenues arising from this collaboration totaling $15,641,000, $21,106,000 and $14,003,000, respectively. As of December 31, 1998, Novartis owned approximately 9% of Isis' outstanding common stock.

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 Isis a $5 million non-refundable pre-commercial fee to partially reimburse us 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. Under the CIBA Vision agreement Isis 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 for $10,000,000. Of that total, $6,000,000 was accounted for as equity and $4,000,000 as deferred revenue. The agreement also provides that Boehringer Ingelheim is entitled to designate 1 person for election to Isis' Board of Directors. As of December 31, 1998 Boehringer Ingelheim owned approximately 9% of Isis' outstanding common stock. Boehringer Ingelheim and Isis are providing equal funding for the combined research and development program and will share equally in the profits from all products of the collaboration. Boehringer Ingelheim has also provided Isis with a $40,000,000 line of credit, available under certain circumstances to be used in support of the combined programs. As of December 31, 1998, the outstanding balance under this line of credit was $22,576,000. The statement of operations for the years ended December 31, 1998, 1997 and 1996 reflects contract revenues of $6,544,000, $5,603,000 and $4,024,000, 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. In 1998, Isis received a total of $3,875,000 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 proprietary antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over the next three years. Isis made the initial $2,000,000 payment in December 1998. 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 at December 31, 1998 was $3,238,000. 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 Zeneca Pharmaceuticals to discover, develop and commercialize novel antisense-based cancer drugs. Under the terms of this collaboration, Isis will create and, with Zeneca, screen antisense-based candidates for certain cancer targets. The agreement specifies that Isis will receive from Zeneca at least $7 million for a technology access fee and annual research finding 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, Zeneca paid $2,000,000 in technology access fees which was accounted for as deferred revenue.

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 will receive from Abbott an upfront fee, 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.

7. EARNINGS PER SHARE

In July 1997, the Financial Accounting Standards Board issued Statement No. 128, "Earnings Per Share." The Company has adopted the provisions of the new standard. In accordance with the statement, prior periods have not been restated as the effect of the change is not material.

The following table sets forth the computation of basic and diluted earnings per share:

	YEAR ENDED DECEMBER 31,		
	1998	1997	1996
Numerator:			
Numerator for basic net loss per share -- net loss	$(42,983)	$(31,066)	$(26,521)
Numerator for diluted net loss per share -- net loss	$(42,983)	$(31,066)	$(26,521)
Denominator:			
Denominator for basic net loss per share -- weighted average shares	26,873	26,456	25,585
Denominator for diluted net loss per share -- weighted average shares	26,873	26,456	25,585
Basic net loss per share	$ (1.60)	$ (1.17)	$ (1.04)
Diluted net loss per share	$ (1.60)	$ (1.17)	$ (1.04)

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. For additional disclosures regarding outstanding stock options and warrants, see Note 4 -- Stockholders' equity.

EXHIBIT 10.23

CONFIDENTIAL TREATEMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(b)(4), 200.83
AND 240.24b-2. * INDICATES OMITTED
MATERIAL THAT IS THE SUBJECT OF A
CONFIDENTIAL TREATMENT REQUEST THAT IS
FILED SEPARATELY WITH THE COMMISSION.

RESEARCH AND DEVELOPMENT

AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

ZENECA LIMITED

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LIST OF EXHIBITS

RESEARCH AND DEVELOPMENT AGREEMENT

THIS RESEARCH AND DEVELOPMENT AGREEMENT (the "Agreement") is made as of the 18th day of December, 1998 by and between Isis Pharmaceuticals, Inc. ("ISIS"), a Delaware Corporation having a principal place of business at 2292 Faraday Avenue, Carlsbad, California 92008, and Zeneca Limited., 15 Stanhope Gate, London W1Y6LN, United Kingdom ("ZENECA").

BACKGROUND

ISIS is engaged in the research and development of therapeutic pharmaceutical products known as antisense oligonucleotides, and ISIS has accumulated considerable knowledge in the field of molecular biology, including processes and techniques relating to the design, investigation and research (including the synthesis) of oligonucleotides and oligonucleotide analogues.

ZENECA has expertise in the research, development, distribution and exploitation of prophylactic and therapeutic treatments for human use.

ZENECA and ISIS wish to establish a collaborative relationship to work jointly with one another with the aim to identify antisense compounds which inhibit the in vivo synthesis of certain biological molecules primarily involved in various disease processes, initially focusing on cancer in humans for ZENECA development and commercialization of products containing such antisense compounds initially focusing on specific targets.

THE PARTIES AGREE AS FOLLOWS:

ARTICLE 1
DEFINITIONS

Capitalized terms used in this Agreement but not otherwise defined will have the meaning set forth in Exhibit A.

ARTICLE 2
RESEARCH PROGRAM; ANNUAL RESEARCH SUPPORT

2.1 Goal of Research Collaboration.

(a) The goal of the Research Collaboration is, through the combined efforts of ISIS and ZENECA scientists and using ISIS and ZENECA technology, to discover Compounds having the potential to be commercialized as drugs for human therapeutic use. The Research Collaboration will be conducted by ISIS and ZENECA and will be managed by the Joint Research Committee.

(b) Research relating to a Target includes the elaboration of necessary cellular, biochemical and molecular-biological approaches (i.e., the development of the knowledge not already available to the two parties, the development and setting up of relevant assays) towards the inhibition of the expression of the protein target molecules by Antisense Technology as well as the conception, design, synthesis and development of therapeutic entities, including the characterization of their biophysical and pharmacokinetic properties. Subject to Section 3.1 the research relating to a Target will explore all reasonable therapeutic applications of a Compound.

(c) The Research Collaboration will include access to all ISIS Technology for purposes of developing Compounds within the terms of article 7 except as described below. The Research Collaboration does not include research relating to or access by ZENECA to ISIS technology or Know-How relating to [*] of oligonucleotides. When and if the Parties decide to include such technology and research in the Research Collaboration, they will negotiate in good faith additional technology access fees to reflect ISIS investment in the technology and an appropriate increase in the Research Payments to fund additional research relating thereto.

(d) ZENECA and ISIS will work together exclusively on the use of Antisense Technology to discover, develop or commercialize antisense inhibitors for any Target for which ZENECA has an Active Target Program. ISIS will not license or assign to a Third Party any ISIS Target Patents relating to a particular target for so long as ZENECA has an Active Target Program for that Target.

2.2 Management of the Research Program.

(a) The Research Collaboration will be managed by a Joint Research Committee composed of 4 members: 2 members to be designated by each party. The initial composition of the Joint Research Committee is set forth in Exhibit C. Each party will be entitled to designate from time-to-time a successor to the member previously designated by it unless the other party has a reasonable objection to such successor.

(b) The Joint Research Committee will hold meetings as necessary but at least twice per year, at times and locations to be mutually agreed upon. The minutes of the meetings will be recorded and marked "confidential" and will be subject to the secrecy obligations and restrictions on use contained in Paragraphs 12.2 and 12.3.

(c) The Joint Research Committee will review and evaluate the work on the Research Collaboration. Its functions will be to decide:

(i) on Targets to be included within the Research Collaboration;

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(ii) on Research Target Profiles for any Target (including any subsequent modifications of such Research Target Profile);

(iii) on therapeutic indications to be pursued for Compounds inhibiting a Target;

(iv) the territorial patenting strategy for Compounds and the "freedom to operate" position by patent due diligence on new Targets or Compounds;

(v) assignment of financial resources and personnel to specific Targets; and/or emphasis among Targets;

(vi) approval of Target-specific Research Plans;

(vii) determination of whether a Compound fulfills the Research Target Profile;

(viii) approval of Excess Research Costs;

(ix) when necessary, on taking appropriate action to adopt alternative approaches or to make recommendations on redirecting or restructuring the Research Plan set out in Exhibit B; and

(x) determine the detailed manufacturing specifications for research Compounds.

(d) The Joint Research Committee will act by unanimous decision. Disputes will be resolved pursuant to Paragraph 13.11 hereof.

2.3 Information and Reports.

ISIS will promptly make available and disclose to ZENECA all information regarding the design, synthesis and screening of lead antisense oligonucleotides for the Targets generated by ISIS in carrying out the Research Collaboration. All discoveries or inventions made by ISIS in undertaking the Research Collaboration will be promptly disclosed to ZENECA. ISIS will keep ZENECA promptly informed of all patenting activities undertaken by ISIS, including without limitation, the opportunity to comment on the specifications filed after any first provisional or priority patent filing on any invention and patent prosecution in PCT, USA, Europe and Japan. ISIS and ZENECA will exchange at a minimum, monthly verbal or written reports, presenting a meaningful summary of the work done under this Agreement. In addition, at ZENECA's request, ISIS will provide written reports of any studies performed by ISIS required to support regulatory submissions to be made by ZENECA, its Affiliates or Sublicensee and will allow ZENECA, its Affiliates or Sublicensees to use the data included in such reports to support such submissions.

2.4 Technology Access Fee; Research Payments.

(a) ZENECA will pay to ISIS [*] million in technology access fees payable as follows:

(i) $2,000,000 payable upon the later of (x) execution of this Agreement or (y) 15 days after execution of the GMO License Agreement;

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(ii) [*] on June 30, 1999;

(iii) [*] payable within 45 days after ISIS first achieves the Technology Milestone.

(b) As payment for the research to be conducted by ISIS in the Research Collaboration, ZENECA will pay to ISIS [*] during the Research Term, in four equal quarterly installments of [*] beginning on the Effective Date and every 3 months thereafter (the "Research Payments"). [*]

(c) Within 12 months of the Effective Date, Zeneca may either add or substitute [*] as an Initial Target in the Research Collaboration pursuant to Paragraph 2.7 hereof. If [*] is added as a Target, [*] . The Joint Research Committee will determine the length of the [*] project and related research payments.

(d) The Research Payments will be applied exclusively to cover only work of the [*] employed in carrying out work under this Research Collaboration [*]. Any studies or work agreed by ZENECA to be conducted outside ISIS, or within ISIS but outside the scope of the Research Plan described in Exhibit B (including, without limitation any ISIS Development Expenses), and any compound to be supplied [*], as described above in any calendar year will be paid for by ZENECA separately, with such costs called "Excess Research Costs." Excess Research Costs will be invoiced by ISIS to ZENECA with payment due within [*] of receipt of invoice. Excess Research Costs for [*] will be billed at [*] (including an appropriate allocation of the costs of process development, analytical development and scale up for such manufacture). [*]

2.5 The Research Term.

(a) The Research Term will be three years beginning with the Effective Date and will be cancelable by ZENECA for any reason at the end of the second year with 6 months prior written notice (i.e., by notice given on or before the 18-month anniversary of the Effective Date). Failure to cancel at the end of the second year will automatically extend the agreement to the full 3-year term; however, the scope of Research Payments for the third year will be mutually agreed to by the Joint Research Committee in light of the agreed Research Collaboration program needs.

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(b) The Research Term may be extended by mutual consent at any time prior to the end of the [*] year for [*] additional extensions of [*] as specified by ZENECA at the time of the extension, based on the program of work agreed to by the Joint Research Committee on the terms contained herein, [*]. The scope of the Research Payments for each subsequent year will be mutually agreed to by the Joint Research Committee in the light of the agreed Research Collaboration program needs. Notwithstanding the foregoing, if the program of work is earlier completed or if the program appears unlikely to be successful, the Parties can, upon mutual agreement, terminate any extension of the Research Term sooner.

2.6 Proposal of Compounds for Development.

(a) During the course of the Research Collaboration, the Joint Research Committee will propose to ZENECA Compounds, which the Joint Research Committee determines meet the Research Target Profile for selection as Development Candidates. ZENECA will have [*] days after receiving the Joint Research Committee's proposal to accept or reject any such Compound.

(b) Within [*] days of [*], ZENECA will pay to ISIS an [*] and ZENECA will have the exclusive right to develop and commercialize such Development Candidate and subsequent Development Candidates inhibiting the same Target as provided herein.

2.7 Rejected Compounds.

(a) Compounds which the Joint Research Committee determines meet Research Target Profile but which are not accepted by ZENECA for development as Development Candidates will continue to be owned in their entirety by ISIS. However, ISIS will not have the right to develop, commercialize or sublicense any such Compounds for so long as ZENECA has an Active Target Program for the Target for such Compound.

(b) [*]

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(c) At the time ZENECA ceases to have an Active Target Program, such Target will be considered an Abandoned Target and ISIS will be free to develop and commercialize any Compound inhibiting such Target fully with, subject to Paragraph 3.4 no further obligation to ZENECA. Notwithstanding the foregoing, ZENECA will retain the right to use any such Compound for internal research purposes.

2.8 Expansion of the Research Collaboration; Substitution or Addition of Targets.

(a) ZENECA may, upon mutual agreement with ISIS, at any time during the first [*] months of the Research Collaboration Term, substitute or add [*] as a Target. [*] may be (i) substituted for one of the other Initial Targets or for any subsequently added Cancer-Related Target for no additional technology access fee and, assuming that the mutually agreed research plan for [*] is similar to that for the Target being substituted, for no additional Research Payments or (ii) added as a Target by initiation of a research program and an increase in the Research Payments which will be agreed by the Joint Research Committee, subject to the Inflation Rate beginning on the second anniversary of the Effective Date. The substitution or addition may occur (i) with [*] months prior notice for a substitution or [*] months prior notice for an addition; and (ii) upon agreement by ZENECA, if required, that the Research Collaboration Term will extend for a period to be determined by the Joint Research Committee to include the term of the Survivin research program following such substitution or addition.

(b) ZENECA may, upon mutual agreement with ISIS at any time during the Research Collaboration Term add additional Cancer-Related Target(s) and subsequently substitute or add such Cancer-Related Target(s) to the Research Collaboration. The substitution or addition to the Research Collaboration may occur (i) with at least [*] months notice for a substitution or addition; (ii) upon agreement by ZENECA that the Research Collaboration Term will continue for at least [*] months following the substitution or addition. If a substitution is made, assuming that the mutually agreed upon research plan for the new Target is similar to that for the Target being substituted, there will be no increase in Research Payments when such substitution is made. Addition of Cancer-Related Targets will require the payment of additional technology access fees [*]. In addition, if the Target is [*], the Parties will agree on additional upfront funding [*]; [*], [*]. If ZENECA designates a desire to add [*]

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[*]

(c) ZENECA may, upon mutual agreement with ISIS at any time during the Research Collaboration Term add additional Non-Cancer-Related Target(s), and subsequently substitute or add such Non-Cancer-Related Target(s) to the Research Collaboration. The substitution or addition to the Research Collaboration may occur (i) with at least [*] months notice for a substitution or [*] months notice for an addition; (ii) upon agreement by ZENECA that the Research Collaboration Term will continue for at least [*] months following the substitution or addition. If a substitution is made, assuming that the mutually agreed upon research plan for the new Target is similar to that for the Target being substituted, there will be no increase in Research Payments when such substitution is made. Addition of non-cancer-related Targets will require the payment of additional technology access fees [*]. If ZENECA designates a desire to add [*].

(d) ISIS and ZENECA will negotiate in good faith any additional terms for the substitution or addition of Targets beyond the Initial Targets. ISIS will have no obligation to substitute or add a Target for one that is subject to active discussions, negotiations or an agreement with a Third Party. ISIS will notify ZENECA of the initiation of discussions with a Third Party regarding Apoptosis Targets unless it is precluded from doing so by confidentiality restrictions.

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(e) For purposes of this paragraph 2.7 "substitution" will mean the termination of a research program relating to one Target and the initiation of a similar research program for the substituted Target. The Target for which the research program is terminated will thereafter be deemed to be an Abandoned Target and the new Target will become a Target for purposes of this Agreement.

2.9 Termination of Research Program for a Target.

(a) ZENECA may at any time after [*] discontinue research relating to any specific Target [*]. The Joint Research Committee will determine the reallocation of the funding for a discontinued Target among the other Targets. For each Abandoned Target, ISIS will be free to continue research on Compounds to inhibit such Target and to use, make, have made and sell the resulting products for such Abandoned Target in accordance with Paragraph 2.7.

(b) Discontinuation of research in a particular Target will not affect the continuation of the Research Collaboration in accordance with its terms.

ARTICLE 3
ZENECA DEVELOPMENT AND COMMERCIALIZATION

3.1 ZENECA Diligence Obligation.

(a) ZENECA will use commercially reasonable efforts to develop a Development Candidate as expeditiously as possible consistent with ZENECA's own practices for drugs of similar commercial potential and for all indications for which ZENECA reasonably determines the Development Candidate is likely to be commercially attractive. If ZENECA determines that it will not develop a Development Candidate for such commercially attractive indication outside of the initial therapeutic focus of the Target as determined by the Joint Research Committee, taking into account ZENECA's overall development plan for the Development Candidate for all indications, ZENECA will reasonably consider development and commercialization of the Development Candidate by ISIS or a Third Party in any indication ZENECA is not pursuing. Such consideration by ZENECA will be intended to maximize the commercial value of the Development Candidate to ZENECA and ISIS without jeopardizing the development or commercialization of the Development Candidate by ZENECA in the indication ZENECA is pursuing. Determination by ZENECA not to permit such commercialization on the grounds that such development could jeopardize the development or commercialization of the Development Candidate shall be deemed to be reasonable.

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(b) ZENECA will use commercially reasonable efforts to commercialize and sell Collaboration Product in each of the Major Countries for all commercially attractive indications as determined by ZENECA in Article 3.1(a) as expeditiously as is reasonable consistent with sound scientific and business judgment and ZENECA's practices with drugs of similar commercial potential. ISIS will provide ZENECA with assistance reasonably requested by ZENECA which will be billed to ZENECA as ISIS Development Cost [*].

(c) If ZENECA fails in its obligations to develop or commercialize a Development Candidate or Collaboration Product under subparagraph (a) or (b) above, at the option of ISIS and after written notice from ISIS and a reasonable opportunity to cure such failure but ZENECA having failed to do this within a reasonable period ZENECA will be deemed to have abandoned such Development Candidate or Collaboration Product and such Compound will become an Abandoned Compound. If such failure relates solely to the failure to commercialize a Collaboration Product in a particular Major Country or if, after written notice from ISIS, ZENECA fails to commercialize a Collaboration Product in a country that is not a Major Country in a manner consistent with ZENECA's typical product launch strategy, the Collaboration Product will become an Abandoned Compound only for that country and ISIS will have the right to commercialize such Collaboration Product in such country whether or not ZENECA has an Active Target Program relating to such Collaboration Product. Failure by ZENECA to adequately develop a Development Candidate or to commercialize a Collaboration Product pursuant to this Paragraph 3.1(c) will not constitute a material breach of this Agreement pursuant to Paragraph 8.2.

3.2 ISIS Diligence Obligation.

ISIS agrees to commit the resources set forth in Paragraph 2.4(c) to exert the efforts necessary and reasonable and consistent with its normal business practices to execute and substantially perform its obligations under the Research Plan, to maintain and utilize the scientific staff, laboratories, offices and other facilities consistent with such undertaking and to reasonably cooperate with ZENECA in the conduct of the Research Collaboration.

3.3 Discontinuation by ZENECA of Development or Commercialization.

ZENECA may discontinue development of any Development Candidate or commercialization of any Collaboration Product by giving written notice to ISIS. Upon such discontinuation, all rights to such Development Candidate will revert to ISIS and be considered an Abandoned Compound. Failure of ZENECA to develop a Development Candidate or commercialize a Collaborative Product pursuant to Paragraph 3.1 will be deemed to constitute discontinuation of

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development or commercialization and the Development Candidate or Collaboration Product will become an Abandoned Compound with or without notice to ISIS hereunder. [*].

3.4 ISIS Right to Develop and Commercialize Abandoned Compounds.

(a) If, and when, ZENECA does not have an Active Target Program relating to an Abandoned Compound or if ISIS has the right to commercialize the Abandoned Compound in a particular country or countries pursuant to Paragraph 3.1 (c), ISIS will be free to develop and/or commercialize such Abandoned Compound.

(b) Following the occurrence of any event described in 3.4(a) above and at ISIS' request, ZENECA will provide in so far it is legally able to do so, and on a non-exclusive basis to ISIS all rights, licenses or other permissions obtained including, without limitation all clinical and preclinical data, regulatory submissions obtained by ZENECA together with, access to ZENECA technology utilized by ZENECA in the development of such Development Candidate both of which exist at the date a Development Candidate becomes an Abandoned Compound and are necessary or useful to continue the development and/or commercialization of such Abandoned Compound, [*]:

STAGE OF COMPOUND ABANDONMENT	ROYALTY
[*]	[*]
[*]	[*]
[*]	[*]
[*]	[*]

Royalties will be paid to ZENECA hereunder on the same basis and terms as royalties are paid to ISIS by ZENECA hereunder.

If ZENECA has incorporated into the Abandoned Compound significant proprietary ZENECA technology or Third Party technology which it may sublicense to ISIS (including, but not limited to, specialized formulation or delivery technology) the Parties will negotiate in good faith an additional royalty for access to such technology, if required.

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3.5 ZENECA Right to Reconsider Abandoned Compounds.

(a) If ISIS pursues the development and/or commercialization of an Abandoned Compound, ZENECA will have a right of first negotiation to reacquire such Abandoned Compound on the earlier of: (i) if ISIS determines that it desires to license such Abandoned Compound to a Third Party (a commercial distribution arrangement will explicitly not be considered a license for these purposes) or (ii) prior to initiation of Pivotal Quality Clinical Study for such Abandoned Compound if ISIS has not licensed rights to a Third Party at that time. If ZENECA desires to be considered a commercial distributor for an Abandoned Product, ISIS will reasonably consider such request.

(b) At the time ZENECA has the right to reacquire an Abandoned Compound, ISIS will provide ZENECA with access to all material data relating to such Abandoned Compound. ZENECA will have [*] following receipt of such information to initiate good faith negotiations with ISIS. Should the Parties fail to reach a mutually agreeable set of terms, ISIS will be free to license the Abandoned Compound to a Third Party on terms no more favorable to such Third Party than those last offered by ZENECA, or to continue on its own to develop and commercialize the Abandoned Compound.

3.6 Shared Compounds.

ZENECA may, at its option, offer to ISIS the opportunity to participate in the joint development and commercialization of a Development Candidate, on a [*].

3.7 Progress Reports.

Beginning on January 30 in the calendar year in which, in the case of ZENECA the first Development Candidate is accepted by ZENECA and in the case of ISIS, an Abandoned Compound is taken into development by ISIS or, if the period following such acceptance to January 30 is less than 6 months, then on the following January 30, each party will submit to the other on each January 30 an annual written progress report summarizing its activities related to product development and clinical evaluation of Development Candidates and Abandoned Compounds as appropriate and the efforts to secure governmental approval to market the Collaboration Products.

3.8 Compulsory Licensing.

If a Third Party seeks a compulsory license for a Collaboration Product in accordance with appropriate provisions of the laws of any country and ISIS and ZENECA agree that the Third Party is legally entitled to such license or the Third

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Party is awarded such license by a decision of the appropriate governmental authority to make such decisions, the granting of such license will not constitute a breach of ISIS' obligations ZENECA will have right to reduce the royalty on sales in such country to an amount no greater than the amount payable by the said Third Party as consideration for the compulsory license.

ARTICLE 4
PAYMENTS FOR DEVELOPMENT CANDIDATES

4.1 Milestone Payments.

(a) Subject to Subparagraph (b) and (d) below, in addition to the other payments required to be made by ZENECA hereunder, ZENECA will pay to ISIS the following amounts with respect to each Development Candidate to reach each milestone:

[*]	[*]
[*]	[*]
[*]	[*]
[*]	[*]

(b) Milestone Payments made for a Development Candidate, which inhibits a specific Target, [*]. Milestone payments [*] for a Development Candidate for which a milestone has already been paid. Milestones [*] in clinical trials [*] for such subsequent Development Candidate at which time, [*] , the previously unpaid milestone payment for the subsequent Development Candidate will be paid.

(c) All milestone payments will be due within 45 days of the milestone being met.

(d) If ZENECA sublicenses development or commercial rights to a Collaboration Product to a Third Party, ZENECA will pay to ISIS the amount ISIS would have received under this Agreement had ZENECA conducted the development or commercialization. If this cannot be achieved within the terms of the proposed sublicense, ZENECA and ISIS will negotiate in good faith payment terms for ISIS which are acceptable to both parties.

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4.2 Royalty.

(a) In consideration of the license rights set forth in Article 7 hereof, ZENECA will pay a royalty to ISIS on each Collaboration Product equal to:

[*] of Net Sales Revenue for the Collaboration Product [*] for such Collaboration Product paid pursuant to Paragraph 4.1(a) [*], and (ii) any royalty [*]; provided, however, that the royalty payment on Net Sales Revenue will not be [*]. Because ISIS will be paying directly to Genzyme Molecular Oncology the royalties owed under the GMO License Agreement, the royalty payable to ISIS hereunder for a Collaboration Product [*] will not be [*] for so long as, and in such territories for which, royalties are owed by ISIS to Genzyme Molecular Oncology under the GMO License Agreement for such Collaboration Product.

(b) The royalties payable hereunder [*].

4.3 Term of Royalty Obligations.

The royalty obligations specified in Paragraph 4.2 will be due and payable and continue as to each Collaboration Product on a country by country basis from the date of First Commercial Sale for the longer of: (i) the term of the last to expire of the ISIS Patents which prevents a Third Party from discovering, developing, making, using or selling such Collaboration Product in that country; [*]. ZENECA will notify ISIS promptly upon introduction of each Collaboration Product in each country. Upon termination of the royalty payment obligation, ZENECA will have, in perpetuity, a fully paid license under the ISIS Technology to discover, develop, make, have made, use, sell, have sold Collaboration Product without further accounting to ISIS.

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4.4 Payments by ZENECA.

Royalties owed by ZENECA to ISIS pursuant to this Article 4 will be paid no later than 45 days after the end of the calendar quarter during which such royalties accrued.

4.5 Currency Conversion.

Royalties will be calculated and paid in United States dollars. For the purpose of computing the Net Sales Revenue made in a currency other than United States dollars, ZENECA will convert such currency from local currency to pounds sterling on a consistent monthly basis using a 5 day average of exchange rates published by Reuters and then convert such pounds sterling to United States dollars monthly using the average of the exchange rate from pounds sterling to United States dollars published by Reuters for the same 5 days provided, however, that with respect to Net Sales Revenue from sales made in a currency other than United States dollars by ZENECA's Affiliates a quarterly exchange rate shall be used for both the conversion from local currency to pound sterling and from pound sterling to United States dollars that is the average of the foregoing exchange rates for each of the three months in the quarter. The foregoing conversion method is in accordance with ZENECA's current accounting policies. In the event ZENECA's policies for currency conversion change in the future, the parties will meet and mutually agree upon a new conversion method.

4.6 Taxation of Payments.

ZENECA will withhold taxes from the royalty or other payments as required by the internal tax law of the U.K. In the case of such withholding being applicable, ISIS may apply for the reduction of rate of withholding tax under the U.K./U.S. Income Tax Treaty with the assistance of ZENECA and, provided the claim is accepted and ZENECA is duly authorized by the Inland Revenue, ZENECA will apply the reduced rate accordingly. If applicable laws required that taxes be withheld, ZENECA will deduct those taxes from the remittable payments, make timely payment of the taxes to the proper taxing authority, and send a confirmation of such payment in a form approved by the UK Inland Revenue to ISIS within 60 days following that payment.

4.7 Interest.

All payments due hereunder from ZENECA that are not paid to ISIS when due and payable as specified in the Agreement will bear interest at an annual rate [*], or at such lower rate of interest as will then be the maximum rate permitted by applicable law.

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ARTICLE 5
MANUFACTURING AND SUPPLY

5.1 Research Supply.

ISIS agrees to supply all of ZENECA's requirements of Development Candidates for its research program under the Research Collaboration in the amounts and in accordance with the specifications set out in Exhibit F.

5.2 Clinical Supply.

ISIS will, if ZENECA requests, supply all of ZENECA's requirements of Development Candidates required for clinical trials [*]. ISIS will supply clinical material on the same basis as research material billed as Excess Research Costs pursuant to mutually agreed upon specifications. ZENECA will provide ISIS with 18-month rolling forecast and a final purchase order [*]. Timing of deliveries will be scheduled consistent with ISIS' other facility requirements and ZENECA's reasonable needs for clinical supply stocking. The Parties will negotiate in good faith the terms of a clinical supply agreement containing these and other customary terms. If ISIS is not able to supply Development Candidates or if ZENECA determines to obtain supply from a Third Party, then ISIS will, at ZENECA's request, promptly transfer all necessary technology and technical assistance [*].

5.3 Commercial Supply.

(a) ZENECA will be free to obtain commercial supply of Collaboration Products from the manufacturer of its choice. If ZENECA desires ISIS to provide commercial supply of Collaboration Products and if ISIS has the capacity and desire to do so, the parties will negotiate in good faith the terms of a commercial supply agreement to be concluded before the initiation of the first Pivotal Quality Clinical Trial.

(b) If ISIS is not able to provide commercial supply or ZENECA determines to manufacture Collaboration Products itself or through an Affiliate or have Collaboration Products manufactured by a Third Party then ISIS will, at ZENECA's request, promptly transfer all necessary technology and technical assistance and grant a [*]

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[*].

5.4 Manufacturing Information.

As reasonably requested by ZENECA, ISIS will provide ZENECA all information in ISIS control relating to Development Candidates and Collaboration Products being developed by ZENECA including without limitation information regarding process, in process control methods, final product characterization/analysis methods, scale, cost and alternative manufacturing sites.

ARTICLE 6

BOOKS AND RECORDS

6.1 Recordkeeping; Audit.

(a) Each party will keep accurate accounts and records in sufficient detail to properly determine the royalties payable to the other under this Agreement for at least 3 years following the end of the calendar quarter to which they pertain.

(b) Each party will make available such accounts and records for inspection during such 3 year period by a certified public accountant retained by the other for such purpose, solely for the purpose of verifying the royalty payments hereunder. Such inspections may be made no more than once in each calendar year, at reasonable times mutually agreed upon by the parties after at least 15 days written notice to the other.

(c) If an audit concludes that additional royalties were owed during the period audited, the party in default will pay the additional royalties within 45 days of the date the other party delivers to it the accounting firm's written report. The fees charged by such accounting firm will be paid by the party initiating the inspection unless the additional royalties owed by the party in default exceed 5% of the royalties paid for the period subject to the audit, in which case that party will pay the fees of the accounting firm.

(d) Each party will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to make reports to the other party, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by the other's independent accountant to the same extent required of the Licensor under this agreement.

(e) Each party will treat all financial information subject to review under this Paragraph 6.1 or under any sublicense agreement in accordance with the confidentiality provisions of this Agreement.

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(f) ISIS will maintain complete and accurate records which are relevant to its expenditure of research manpower provided under this Agreement pursuant to the Research Plan. With reasonable notice, said records will be open during reasonable business hours for a period of from [*] for examination at ZENECA's expense by an independent certified public accountant appointed by ZENECA and reasonably acceptable to ISIS. Such examination will be for the sole purpose of verifying for ZENECA the cost of the research conducted and whether or not funds received by ISIS from ZENECA were used for conducting the research.

ARTICLE 7
LICENSE GRANTS

7.1 License for Collaboration Products.

In consideration of the payments made under Paragraphs 2.6, 4.1 and 4.2:

(a) ISIS hereby grants to ZENECA and its Affiliates during the term of the Collaboration a co-exclusive (with ISIS), worldwide, non-transferable royalty free license under the GMO License Agreement subject to the terms of this Agreement, solely to the extent necessary or appropriate to carry out ZENECA's responsibilities under this Agreement.

(b) Upon payment by ZENECA of the milestone payment due on [*] for a Collaboration Product, ISIS will grant to ZENECA (i) a worldwide exclusive, sublicensable license under the portions of the ISIS Technology necessary to make, have made, use and sell such Collaboration Product and the right to sue any Third Party for any act of infringement of any such portion of the ISIS Technology in the event that the Third Party infringes an ISIS Target Patent under this 7.1(b), (ii) a worldwide, exclusive, sublicensable license to the ISIS Target Patents relating to the Target of the Collaboration Product to make, have made, use and sell such Collaboration Product and to sue any Third Party for any act of infringement within the scope of the claims of such ISIS Target Patent. If ZENECA reasonably determines that it is necessary for it to obtain the licenses granted hereunder [*] in order to allow sublicensing in a territory in which ZENECA cannot reasonably develop or commercialize on its own, ISIS will grant such licenses upon notice from ZENECA of its requirement and an agreement from ZENECA to pay ISIS any additional expenses incurred by it for example, fees required to convert patents and/or patent applications to Large Entity status.

(c) Nothing contained herein will be deemed to grant a license to any technology not owned or controlled by ISIS or to any technology of which ISIS is a licensee but for which ISIS is prohibited from granting sublicenses all which technology existing at the date of this Agreement is identified in Exhibit G.

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(d) For any technology acquired by ISIS from a Third Party before the Effective Date (which is described in Exhibit G) or after the Effective Date which is necessary or useful to make, use or sell a Collaboration Product, before such technology is included in any license granted pursuant to Paragraph 7.1(a), ZENECA and ISIS will negotiate a mutually agreeable set of terms for the inclusion of such technology, which terms will consider the cost to ISIS to acquire and develop such technology as well as any milestone or royalty payments ISIS may owe to the licensor with respect to such technology. The Parties acknowledge and agree that the Patents licensed to ISIS pursuant to the GMO License Agreement are included herein under the terms contained herein with no additional negotiation.

(e) ISIS will not take any action after the Effective Date that would encumber its technology in any way that would impair its ability to grant the licenses contemplated hereunder.

(f) ZENECA agrees that the rights and licenses granted hereunder do not provide to ZENECA the right to use ISIS Technology for any purpose except as expressly provided in this Paragraph 7.1.

ARTICLE 8
TERM AND TERMINATION

8.1 Term.

This Agreement will be in effect beginning the Effective Date and, unless otherwise terminated by operation of law or by acts of the Parties in accordance with the terms of this Agreement, will remain in effect until the last to expire of any royalty obligation under Paragraph 4.2. Provided, however, that if the GMO License Agreement is not executed by January 31, 1999, in accordance with Exhibit H, in so far as is necessary to protect ZENECA's freedom-to-operate hereunder with respect to the patents covered thereby, ZENECA will have the right to terminate the Agreement or, at its option, to initiate renegotiation of the Agreement.

8.2 Termination by Either Party.

(a) Termination for Breach.

In the event of either Party being in default of any material obligation contained in this Agreement and failing to cure or obtain the cure of such breach within 60 days after receipt of written notice thereof from the non-defaulting party (45 days in the case of any payment required to be made hereunder); provided, however, that if the defaulting party is unable to cure a breach for causes beyond its reasonable control, then such sixty-

day period will be extended for a period of time reasonable under the circumstances as long as the defaulting party is continuing to pursue such a cure in good faith; provided, further that in the event of a good faith dispute about payment amounts, the party allegedly owing the money may deposit any contested amount (but not the uncontested portion, which must be paid) in an interest bearing escrow account pending resolution of such contest, with the prevailing party receiving both principal and interest upon resolution.

(b) Notwithstanding the foregoing, in the event of an uncured material breach by one party the non-breaching party may choose not to terminate this Agreement and to continue it in full force with all of the rights and obligations of the Parties continuing in place and may rely in stead on a damage remedy to compensate for the effects of the breach.

8.3 Termination for Bankruptcy.

The institution by or against either party of proceedings to be adjudicated as bankrupt or insolvent or to be reorganized or released under any bankruptcy or equivalent statute applicable to that party, the appointment of a receiver, liquidator or trustee, or the making of an assignment for the benefit of creditors; provided, however, that if any such proceeding is instituted without the consent or acquiescence of that party against whom such order is made, this Agreement may not be terminated if such party causes such proceedings to be dismissed within 60 days from the date the proceeding was instituted.

8.4 Termination By ZENECA Without Cause.

After the Research Collaboration Term as defined in Paragraph 2.5, ZENECA may terminate this Agreement by written notice to ISIS.

8.5 Effects of Termination.

Upon termination of this Agreement by ISIS or ZENECA pursuant to Paragraph 8.2 or 8.3, all rights and licenses granted by ISIS to ZENECA will terminate and the right to develop Development Candidates and to commercialize Collaboration Products will revert to ISIS.

ARTICLE 9
INVENTIONS AND PATENTS

9.1 Inventions.

ISIS will retain title to inventions, whether or not patentable, made solely by employees of or consultants to ISIS, and to patents thereon. ZENECA will retain

title to inventions, whether or not patentable, made solely by employees of or consultants to ZENECA and to patents thereon. ISIS will hold title to all inventions, whether or not patentable, made jointly by employees of or consultants to ISIS and ZENECA and to patents thereon.

9.2 Patents.

ISIS will be responsible to diligently file, prosecute and maintain in force and defend in those countries in the world determined by the JRC all patent applications and patents for ISIS Target Patents. [*]. If ISIS declines to apply for or decides to abandon any ISIS Target Patent and relinquish its rights thereunder in any particular country, it will promptly notify ZENECA in writing and ZENECA will have the right to assume responsibility for maintaining such patent application or patent, at its own expense and in its own name. ISIS agrees to cooperate with ZENECA so as to enable ZENECA to undertake such maintenance without loss of patent rights. ZENECA will have complete responsibility for such continued maintenance and may, in its sole discretion, allow any such patent application or patent to lapse at any time.

9.3 Patent Marking.

ZENECA, its Affiliates and Sublicensees will mark all Collaboration Products made, used or sold under the terms of this Agreement, or their containers, in accordance with the applicable patent marking laws, as required.

9.4 Defense of Patent Infringement Suits.

(a) Notwithstanding the foregoing, [*]. The Parties acknowledge that any royalty owed to Genzyme Molecular Oncology under the GMO License Agreement will be paid by ISIS to Genzyme Molecular Oncology [*].

(b) In the event that (i) ZENECA's use, as set forth in this Agreement, of any ISIS Technology licensed under this Agreement infringes or is likely to infringe any patent or other intellectual property rights of any Third Party, (ii) such infringement is likely to prevent ZENECA from selling Commercial Products, and (iii) at the time a Compound is proposed by the Join Research Committee as a Development Candidate, ISIS has not informed ZENECA in writing of the existence of such potential patent infringement then, and only to the extent that ZENECA is required to pay royalties or other payments to a Third Party, [*], but in no event will ISIS' royalty be reduced to less than [*] in any calendar year.

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(c) In the event that (i) the discovery, development, manufacture, use or sale of a Collaboration Product is determined by ZENECA in its reasonable estimation to have infringed or to be likely to infringe any patent of any Third Party, and (ii) such infringement is not covered by Paragraph 9.4(b), then, and only to the extent that ZENECA is required to pay royalties or other payments to a Third Party. ISIS and ZENECA will discuss in good faith reducing the royalty payable by ZENECA to ISIS under this Agreement.

(d) If a Third Party asserts that the manufacture, use or sale of any Collaboration Product infringes a patent owned or controlled by a Third Party, ZENECA will be solely responsible for defending and settling in its sole discretion against any such assertions. ISIS will provide all reasonable assistance requested by ZENECA to defend or settle such action. ISIS will have the right at its own expense to participate in such suit at its own expense.

(e) The Parties acknowledge that, under certain licenses listed on Exhibits G-1 and G-3 and other licenses that Isis may acquire in the future and which ISIS shall notify ZENECA of in writing, royalties might owe to parties from whom ISIS has acquired nonsublicensable licenses if ISIS is not the manufacturer of a Collaboration Product and no royalty reduction will be made by reason of these royalties.

9.5 Suits for Third-Party Infringement.

(a) Each party will advise the other promptly upon its becoming aware of any third party infringement of an ISIS Target Patent. ISIS agrees, within reasonable business judgement and at its own discretion, to promptly take such action as is required to restrain such infringement at its own cost. ZENECA will cooperate fully with ISIS at ISIS' expense in ISIS' attempt to restrain such infringers. ZENECA may be represented by counsel of its own selection at its own expense at any suit or proceeding brought by ISIS to restrain such infringement. ISIS will bear the expense of any suit or suits and will obtain all benefits of the recoveries from such suit or suits, whether by judgment, award, decree or settlement up to an amount equal to [*]

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[*] and the remainder will be allocated among ISIS and ZENECA in a manner reasonably calculated to correspond to the relative distribution of profits on the Collaboration Product(s) to which such recovery pertains between ISIS and ZENECA.

(b) If, within 14 days of becoming aware of a third party infringement under 9.5(a), ISIS fails to institute an infringement suit that ZENECA feels is reasonably required, ZENECA will have the right, at its own discretion, to institute an action for infringement. ZENECA will bear the expense of any such suit or suits and will obtain all of the benefits of the recoveries from such suit or suits, whether by judgement, award, decree or settlement up to an amount equal to [*] and the remainder will be allocated among ISIS and ZENECA in a manner reasonably calculated to correspond to the relative distribution of profits on the Collaboration Product(s) to which such recovery pertains between ISIS and ZENECA. Should ZENECA bring any such suit, ISIS will cooperate in all reasonable ways with ZENECA in any such suit or suits at ISIS' expense. ISIS may be represented by counsel of its own selection at its own expense

(c) If the parties agree to mutually share expenses and to pursue an infringement suit together, they will (i) share in any and all benefits in the recovery from such suit, whether by judgment, award, decree or settlement in the manner mutually agreed among them, and (ii) agree on the lead plaintiff, selection of counsel and other litigation strategy matters.

ARTICLE 10
WARRANTIES AND DISCLAIMERS

10.1 Representations and Warranties.

(a) Each party warrants to the other party that it is free to enter into this Agreement and carry out its obligations hereunder, and that its execution and delivery of this Agreement and performance of its obligations hereunder will not violate, be in conflict with, or constitute a default (or an event which, with notice or lapse of time or both, would constitute a default) under any agreement to which it is party or by which it is bound.

(b) Each party warrants to the other that, to the best of its knowledge, its use (or use by the other party under this Agreement) of its existing technology does not infringe any issued patent of any Third Party of which it is aware, and it has not received any communication alleging that it has infringed or acted in conflict with, or by conducting its business as proposed, would infringe or act in conflict with the right of any Third Party.

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(c) Neither Party has granted, nor during the term of the Agreement will grant, any right to any Third Party relating to its respective technology which would conflict with the rights granted to the other Party in this Agreement.

(d) Notwithstanding the foregoing, both parties acknowledge that Genzyme Molecular Oncology has certain issued patents and patent applications that ISIS is in the process of licensing under the terms of the GMO License Agreement. Nothing contained in either Party's representations will be deemed to be made without recognition of the existence of these patents.

10.2 Disclaimer.

ALL ITEMS, INFORMATION AND MATERIALS PROVIDED TO ZENECA BY ISIS HEREUNDER ARE TO BE USED BY ZENECA FOR INVESTIGATIONAL PURPOSES ONLY. NEITHER PARTY MAKES ANY WARRANTIES, EXPRESS, IMPLIED, STATUTORY OR OTHERWISE, OF ANY KIND, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

ARTICLE 11
INDEMNITY AND INSURANCE

11.1 Indemnity.

(a) Each Party (the "Indemnifying Party") will indemnify, defend and hold the other Party (the "Indemnified Party") harmless from and against any and all liabilities, claims, damages, costs, expenses or money judgments incurred by or rendered against the Indemnified Party and its Affiliates and sublicensees arising out of any injuries to person and/or damage to property resulting from (a) negligent acts of the Indemnifying Party performed in carrying out its obligations hereunder, including failure by the Indemnifying Party to provide the Indemnified Party with any information of the Indemnifying Party's which, if timely received would have avoided injury, death or damage, provided such failure to provide such information is due to negligence on the part of the Indemnifying Party, and (b) personal injury to the Indemnified Party's employees or agents or damage to the Indemnified Party's property resulting from acts performed by, under the direction of, or at the request of the Indemnifying Party in carrying out activities contemplated by this Agreement.

(b) In addition to its obligations in Paragraph 11.1(a) hereof, ZENECA will indemnify and hold ISIS harmless from and against any and all liabilities, claims, damages, costs, expenses or money judgments which result from the manufacture (other than manufacture by ISIS), use, promotion and sale of Development Candidates or Collaboration Products under this Agreement.

(c) The Indemnifying Party's obligations hereunder as to any claim are subject to (i) its being given prompt notice thereof; (ii) the sole right to control the defense and settlement; and (iii) the lack of negligence or willful misconduct leading to the claim by the Indemnified Party.

11.2 Insurance.

Each Party will obtain and maintain, in all places in which Collaboration Products are developed, used or sold, product liability insurance in the amounts and with the deductibles customarily maintained by that party and which are consistent with its obligations with respect to the products sold. Each Party will provide to the other information concerning the existence of such insurance upon request from time to time.

ARTICLE 12
TRADENAMES, TRADEMARKS, CONFIDENTIALITY AND PUBLICATIONS

12.1 Tradenames and Trademarks.

Nothing contained in this Agreement will be construed as conferring any right of one Party to use in any manner any tradename or trademark of the other Party or any of its Affiliates without such other party's prior written consent and approval as to form.

12.2 Confidentiality.

ZENECA and ISIS agree for themselves, and for their Affiliates and Sublicensees, and on behalf of their respective officers, employees and agents, that for the greater of five years following the expiration or termination of this Agreement or fifteen years from the Effective Date, each will treat as confidential, using the maximum degree of care that it uses for its own proprietary information, and that it will not use (except as permitted under this Agreement) for its own benefit or the benefit of any third party, any of the Confidential Information furnished to it by the other party unless the furnishing party otherwise agrees in writing or unless the party receiving the Confidential Information is required to disclose such Confidential Information to a court of law or to appropriate governmental agencies to enable the recipient to secure governmental approval of a Collaboration Product. In each such case, the recipient will notify the disclosing party of the requirement and work together with the disclosing party to obtain the maximum amount of confidentiality provided by such court of law or governmental agency.

12.3 Shared Confidential Information.

In the course of performance of this Agreement, the Parties may jointly develop, invent or discover information, which will be considered to be the "Shared

Confidential Information" of both Parties. Each Party agrees that it will take the same steps to protect the confidentiality of the Shared Confidential Information as it takes to protect its own proprietary and confidential information.

Each Party will protect and keep confidential and will not publish or otherwise disclose to any Third party, except as contemplated by this agreement or with the other Party's written consent, the Shared Confidential Information for the same period which covers the Confidential Information. Each Party may, however, use any Shared Information for any purpose provided that such use will not be deemed a license or grant of any additional right or license other than or in addition to the rights and licenses granted in this Agreement.

This Paragraph 12.2 and 12.3 supersedes any confidential disclosure agreement between the Parties as to the subject matter hereof. Any confidential information under such agreement will be treated as Confidential Information hereunder.

12.4 Publications.

ISIS and ZENECA agree to discuss the timely publication in respected scientific journals of articles prepared by their respective researchers relating to such researchers' work on Development Candidates or Collaboration Products with a view toward resolving the competing interests of confidentiality and desired scientific credit through publication. The manuscript of each proposed publication will first be submitted to both parties and if either Party advises within 30 days of receipt of the manuscript that publication of particular information would materially diminish the commercial value of a Development Candidates or Collaboration Products, publication of such information will be delayed for such time as the parties agree, in order to permit the preparation of patent applications or other documents to protect the commercial interests of the parties. The Parties acknowledge that publication delay may be beneficial to ensure that patent filings contain appropriate support and, as a result, the Party whose invention is involved will inform the other of the time reasonably required to ensure an optimal patent coverage strategy and both parties agree to abide by that decision. Notwithstanding the foregoing, there will be no publication of any Confidential Information or Shared Confidential Information reasonably valuable to ISIS or ZENECA without the agreement of both ISIS or ZENECA.

ARTICLE 13
MISCELLANEOUS

13.1 Bankruptcy.

All rights and licenses granted under or pursuant to this Agreement by ISIS to ZENECA are, and will otherwise be deemed to be, for purposes of Section 365(n) of Title 11, U.S. Code (the "Bankruptcy Code"), licenses of rights to "intellectual property" as defined under section 101(60) of the Bankruptcy Code. The Parties

agree that ZENECA, as a licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the Bankruptcy Code. ISIS agrees during the term of this Agreement to create and maintain current copies or, if not amenable to copying, detailed descriptions or other appropriate embodiments, of all such intellectual property. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against ISIS under the Bankruptcy Code, ZENECA will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in its possession will be promptly delivered to ZENECA (a) upon any such commencement of a bankruptcy proceeding upon written request therefore by ZENECA, unless ISIS elects to continue to perform all of its obligations under this Agreement or (b) if not delivered under (a) above, upon the rejection of this Agreement by or on behalf of ISIS upon written request therefore by ZENECA.

13.2 Waiver.

No waiver by either party hereof of any breach or default of any of the covenants or agreements herein set forth will be deemed a waiver as to any subsequent or similar breach or default.

13.3 Assignment.

This Agreement will be binding upon and inure to the benefit of the parties hereto and their successors and assigns; provided, however, that neither party will assign any of its rights and obligations hereunder to a non-Affiliate without the consent of the other party which consent will not be withheld unreasonably except as incident to the merger, consolidation, reorganization, or acquisition of stock or assets affecting substantially all of the assets or actual voting control of the assigning party with regard to the business unit to which this Agreement relates.

13.4 Notices.

Any notice or other communication required or permitted to be given to either party hereto will be in writing and will be deemed to have been properly given and to be effective on the date of delivery if delivered in person or by telex or facsimile or 2 business days after mailing by expedited delivery or 5 days after mailing by registered or certified mail, postage paid, to the other party at the following address:

In the case of ISIS: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: CEO (Fax: 760-931-0265)
With copy to: B. Lynne Parshall
(Fax: 760-431-9448)

In the case of ZENECA	Zeneca Pharmaceuticals Attention: The Legal Director Alderley House, Alderley Park, Macclesfield Cheshire SK10 4TF. Attention: Legal Director (Fax: [*])

Either party may change its address or fax number for communications by a notice to the other party in accordance with this Paragraph 13.4.

13.5 Governing Law.

This Agreement will be interpreted and construed in accordance with the substantive laws of the State of Delaware. ZENECA and ISIS hereby submit to the jurisdiction and venue and procedural rules of the United States District Courts for the State of Delaware for any action hereunder that is permitted consistent with Paragraph 13.11. ZENECA and ISIS agree that service of process may be effected against each of them by certified or registered mail with respect to legal actions commenced in any such jurisdiction by the other, its successors or assigns.

13.6 Amendment.

No amendment or modification hereof will be valid or binding upon the parties unless made in writing and signed by both parties.

13.7 Force Majeure and Hardship.

(a) Any delays in performance by any party under this Agreement will not be considered a breach of this Agreement if and to the extent caused by occurrences beyond the reasonable control of the party affected, including but not limited to acts of God, embargoes, governmental restrictions, strikes or other concerted acts of workers, fire, flood, explosion, riots, wars, civil disorder, rebellion or sabotage. The party suffering such occurrence will immediately notify the other party and the time for performance of any obligation hereunder, except the due diligence obligations set forth in Paragraph 3.1, will be extended by the actual time of delay caused by the occurrence.

(b) If for reasons unforeseen at the Effective Date the performance of this Agreement becomes an undue burden for either party the parties will in good faith negotiate for an appropriate amendment hereof with a view to alleviating or eliminating said burden.

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13.8 Independent Contractors.

Nothing contained in this Agreement will be construed to create an agency, partnership or employer and employee relationship between ISIS and ZENECA. At no time will one party make commitments or incur any charges or expenses for or in the name of the other party except as specifically provided herein.

13.9 Severability.

If any term, condition or provision of this Agreement is held to be unenforceable for any reason, it will, if possible, be interpreted rather than voided, in order to achieve the intent of the parties to this Agreement to the extent possible. In any event, all other terms, conditions and provisions of this Agreement will remain valid and enforceable to the full extent.

13.10 Entire Agreement.

This Agreement when they are executed embody the entire understanding of the parties with respect to the subject matter of this Agreement and will supersede all previous communications, representations or understandings, either oral or written, between the parties relating to the subject matter hereof.

13.11 Dispute Resolution.

Any dispute or claim arising out of or in connection with the Agreement will be resolved as follows: (i) for a period of 30 days after a dispute arises the CEO of ISIS and the Research and Development Director of ZENECA Pharmaceuticals business will negotiate in good faith in an effort to resolve the dispute and (ii) if the dispute has not been resolved at the close of such 30 day period, the matter will be finally settled by binding arbitration under the Rules of Arbitration of the American Arbitration Association, by their arbitrators appointed in accordance with said rules; provided that if the parties cannot agree on who is to serve as the arbitrator, each party will appoint one nominee and those nominees will in turn jointly appoint the third arbitrator. Arbitration will take place in Delaware. The costs of the arbitration, including administrative and arbitrators' fees, will be shared equally by the parties; provided, that each party will bear the costs of its own attorneys' fees and expert witness fees. Judgment on an award rendered by an arbitrator or arbitrators may be entered in any court having jurisdiction thereof. Notwithstanding the foregoing, the parties may apply to any court of competent jurisdiction for preliminary or interim equitable relief without breach of this arbitration provision.

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13.12 Government Approvals.

The Parties agree to make all filings with governmental agencies as shall be required by law in connection with this Agreement and the activities contemplated hereunder.

IN WITNESS WHEREOF, the Parties have executed this Agreement, in duplicate originals, by their respective officers hereunto duly authorized, as of the day and year hereinabove written.

Isis Pharmaceuticals, Inc.

BY _____
B. Lynne Parshall
Title: Executive Vice President

Zeneca Limited

By _____
C.R.W. Petty
Title: Legal Director, Authorized Signatory

EXHIBIT A
DEFINITIONS

1.1 "ABANDONED COMPOUND" means a Development Candidate which ZENECA subsequently ceases to develop or commercialize pursuant to Paragraph 3.1(b) or 3.3.

1.2 "ABANDONED TARGET" means (i) any Target for which another Target is substituted pursuant to Paragraph 2.8; (ii) any Target following termination of the research program for such Target; and (iii) all Targets upon termination of the Research Collaboration.

1.3 "ACTIVE TARGET PROGRAM" means (i) an ongoing research program as part of the Research Collaboration on the Target; (ii) an active clinical development program for a Development Candidate inhibiting such Target; or (iii) a marketing and commercialization program for a Collaboration Product inhibiting such Target.

1.4 "AFFILIATE" means, as to ISIS, any corporation, company, partnership, joint venture or firm which controls, is controlled by, or is under common control with, ISIS; and, as to ZENECA, any enterprise which, directly or indirectly, is controlled by ZENECA alone or together with partners of ZENECA or partners of ZENECA alone, as long as such control exists. For the purpose of the preceding sentence, the word "control" means the ownership of at least 50% of the outstanding voting stock of such enterprise or, a comparable equity interest in any other type of entity.

1.5 "ANTISENSE TECHNOLOGY" means the selective inhibition of protein synthesis at the nucleic acid level. This inhibition is caused by the binding of an oligonucleotide or an analog thereof (termed "oligonucleotide") to the complementary sequence. In particular, an oligonucleotide will specifically bind to the sequence of the selected messenger or viral RNA by base-pairing and will hence bring about a selective inhibition of gene expression.

1.6 "[*] " means those molecular targets which play a direct role in regulation of [*] and for which inhibitors are anticipated to provide a positive therapeutic benefit in the treatment of [*]. Targets covered are: [*].

1.7 "CANCER-RELATED TARGETS" means Targets added to the Research Collaboration pursuant to Paragraph 2.8 whose primary therapeutic use is the treatment of cancer.

1.8 "COLLABORATION PRODUCT(S)" means a Development Candidate which ZENECA commercialize itself or through its Affiliate or Sublicensees.

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1.9 "COMPOUNDS" means any oligonucleotide or analogs designed using Antisense Technology for use as a human therapeutic to inhibit a Target as part of the Research Collaboration.

1.10 "CONFIDENTIAL INFORMATION" means any confidential information including, without limitation, information which is disclosed by one party to the other relating to any technology research project, development project or plan, manufacturing process, technology or plan, marketing or commercial plan, financial or personnel matter relating to either Party, its present or future products whether within or outside the Collaboration, whether in oral, written, graphic or electronic form. Confidential Information will not include information which:

(a) is or will have been known to the receiving party prior to the disclosure by the other party as evidenced by written record or other proof; or

(b) is or will have been public knowledge through no fault of the receiving party; or

(c) has been received from a Third Party who did not acquire it directly or indirectly from the disclosing party; or

(d) is independently developed by the receiving party without the use of or reference to information disclosed by the other party.

The material financial terms of this Agreement constitute Confidential Information.

1.11 "DEVELOPMENT CANDIDATE" means a Compound and formulation which meets the Research Target Profile and is accepted for development by ZENECA. Chemical modifications to a Development Candidate or materially different formulations that have a significant effect on the commercial desirability of the Development Candidate will be considered separate Development Candidates.

1.12 "EFFECTIVE DATE" means December 18, 1998.

1.13 "EXCESS RESEARCH COSTS" means the costs of the Research Collaboration in addition to Research Payments described in subparagraph 2.4(b). Excess Research Costs for compound supply in excess of [*] per compound per calendar year or [*] of all compounds per calendar year will be billed at [*] of the sum of ISIS' actual cost of raw materials for such compound plus ISIS' Personnel Fully Burdened Rate for such manufacture (including an appropriate allocation of costs of process development, analytical development and scale up for such manufacture). Excess Research Costs for outside expenditures will be billed at [*]. Excess Research Costs for ISIS performance outside the tasks outlined in the Research Plan will be billed at ISIS' Personnel Fully Burdened Rate.

1.14 "FDA" means the United Stated Food and Drug Administration or an equivalent agency in a Major Country.

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1.15 "FIRST COMMERCIAL SALE" means the first transfer for value of title to a Collaboration Product by ZENECA, its Affiliates or Sublicensees to a non-Affiliate for consideration in any arm's length transaction or the first use (excluding the supply of clinical trial materials) of a Collaboration Product by ZENECA, its Affiliates or Sublicensees in a country following Governmental Approval in such country, whichever occurs first. For the purpose of this definition all transfer of title to reasonable quantities of any free samples of Collaboration Product or to clinical trial material shall not constitute a First Commercial Sale.

1.16 "GMO LICENSE AGREEMENT" means a non-exclusive license agreement with Genzyme Molecular Oncology to license certain [*] patents having the terms attached hereto as Exhibit H.

1.17 "IND" means the regulatory filing required to initiate Phase I Clinical Trials in the US or any other country. If Phase I Clinical Trials are initiated without a requirement for regulatory filing or approval an IND will be deemed to have been filed on initiation of Phase I Clinical Trials.

1.18 "INFLATION FACTOR" will mean an annual adjustment based upon changes in the Consumer Price Index for Urban Wage Earnings and Clerical Worker - U.S. City Average, for the prior 12 months, rounded up to the nearest $5,000 per FTE.

1.19 [*].

1.20 "ISIS DEVELOPMENT EXPENSES" means costs incurred by ISIS to conduct, at ZENECA's request, additional work on a Compound after it has been designated a Development Candidate and will include ISIS labor, billed at the ISIS Personnel Fully-Burdened Rate (which will include overhead items such as operating leases, rents, equipment, supplies and related departmental and company overhead) plus outside expenses including the cost of raw materials for compound supply, clinical grants, laboratory work, CRO, outside data management charges, charges for outside pharmacokinetic, toxicological and other testing, and an appropriate allocation of all manufacturing functions which directly benefit a Development Candidate including process development and analytical research and development.

1.21 "ISIS KNOW-HOW" means all proprietary inventions, technology, trade secrets, clinical and preclinical results (collectively, "inventions") discovered or developed by ISIS prior to the Effective Date which are necessary or useful to make, use or sell Collaboration Products and which are not covered by ISIS Patents. ISIS Know-How will also include any inventions which are not covered by ISIS Patents which are necessary or useful to make, use or sell Collaboration Products, discovered or developed by ISIS after the Effective Date or acquired by ISIS from

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Third Parties before or after the Effective Date provided that ISIS is free to license such inventions to ZENECA, and, provided further, that if ISIS developed or acquired such inventions for or from a Third Party, ISIS and ZENECA have mutually agreed on the terms upon which ISIS will provide such inventions to ZENECA, as provided for in Paragraph 7.1(c).

1.22 "ISIS PATENTS" means any and all patents, both foreign and domestic, which relate to inventions made by ISIS on or prior to the Effective Date which are necessary or useful to make, use or sell Collaboration Products including without limitation ISIS Target Patents. ISIS Patents will also include any patents relating to inventions made by ISIS after the Effective Date or licensed to ISIS before or after the Effective Date which are necessary or useful to make, use or sell Collaboration Products, provided that ISIS is free to license such patents to ZENECA and, provided further, that if ISIS developed or acquired such inventions for or from a Third Party, ISIS and ZENECA have mutually agreed on the terms upon which ISIS will provide such patents to ZENECA as provided in Paragraph 7.1(c). Notwithstanding the foregoing, ISIS Patents will include any Patents licensed to ISIS under the GMO License Agreement with no further payments required except as expressly provided in this Agreement. "Patents" as used herein will include, without limitation, all substitutions, extensions, reissues, renewals, divisions, continuations, continuations-in-part, inventors' certificates and all foreign counterparts of the aforementioned. Attached hereto as Exhibit G is a list of all ISIS' licenses as of the Effective Date that may be relevant to the Research Collaboration including the technology covered and the royalty rate.

1.23 "ISIS PERSONNEL FULLY-BURDENED RATE" means [*].

1.24 "ISIS TARGET PATENTS" means claims of ISIS Patents arising out of inventions made by ISIS during the Research Collaboration which cover specific antisense compounds directly inhibiting a particular Target.

1.25 "ISIS TECHNOLOGY" means ISIS Patents, ISIS Target Patents and ISIS Know-How.

1.26 "JOINT RESEARCH COMMITTEE" means the Committee defined in Paragraph 2.2.

1.27 "MAJOR COUNTRY" means the United States, Japan, the Federal Republic of Germany, France, the United Kingdom or other European Community country if chosen by ZENECA to be rapporteur country for the Hi-Tech product registration procedure within the European Community.

1.28 "NDA" means a New Drug Application filed with FDA after completion of clinical trials to obtain marketing approval for a commercial product in the United States or equivalent application for regulatory approval in other countries.

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1.29 "NET SALES REVENUE" means the total invoiced amount of all sales of Collaboration Product by ZENECA its Affiliates or Sublicensees less:

i) Prompt payment or other trade or other quantity discounts, rebates or retroactive price reductions actually allowed and taken in such amounts as are customary in the trade;

ii) Commissions paid or allowed to distributors and agents who are independent Third Parties other than such parties who are performing detailing functions;

iii) Amounts repaid or credited by reason of timely failure or rejection or recalls (whether voluntary or mandatory);

iv) Customs, duties and taxes (other than franchise or income taxes on the income of ZENECA) actually paid or withheld;

v) Allowances [*] in any period including any allowances for bad debt, provided that upon the extinguishment of any such allowance, the extinguishment will be determined to be a receipt; and

vi) Transportation and delivery charges [*] in any period, including insurance premiums.

Net Sales Revenue shall exclude:

i. The transfer of reasonable and customary quantities of free samples of Collaboration Product, clinical trial materials and sales to an Affiliate or a Sublicensee, other than for subsequent resale.

ii. Sales or transfers of Collaboration Product among ZENECA and its Affiliate unless the receiving party is the consumer or user of the Collaboration Product.

iii. Use by ZENECA, its Affiliates or Sublicensees of Collaboration Product for any use connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary marketing approvals for Collaboration Product.

If ZENECA, its Affiliates or Sublicensees intend to use a Collaboration Product rather than resell it, the sales price for such Product will be calculated based on the average of the sales of Collaboration Product to Third Parties during the period in which such Collaboration Product is transferred to such Affiliate or Sublicensee and included in Net Sales Revenue as if sold to a Third Party at such price during such period.

Net Sales Revenue will be calculated in U.S. dollars in accordance with Paragraph 4.5.

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1.30 "NON-CANCER-RELATED TARGETS" means Targets added to the Research Collaboration pursuant to Paragraph 2.8(c) whose primary therapeutic use is the treatment of a disease or diseases other than cancer.

1.31 "PARTY" means ISIS or ZENECA, or ISIS and ZENECA.

1.32 "PHASE II CLINICAL TRIALS" means the initial clinical testing of a Compound in humans who are patients with a disease for which the Compound is being tested with the intention of gaining a preliminary assessment of the safety, efficacy and dosing regimen of a Compound in treating such disease.

1.33 "PIVOTAL QUALITY CLINICAL TRIAL" will mean a human clinical trial of a Compound designed to be of a size and statistical power to support an NDA Filing alone or in combination with other studies. If it is unclear whether or not a study design will be sufficient to support an NDA Filing (other than by virtue of the uncertainty of efficacy data from that trial) the study will be deemed to be a Pivotal Quality Trial on the initiation of activities to support an NDA Filing. Initiation of a Phase III clinical study will be deemed to be initiation of a Pivotal Quality Study.

1.34 "RESEARCH COLLABORATION" means the collaboration between ISIS and ZENECA to discover antisense drugs as defined in this Agreement.

1.35 "RESEARCH PAYMENTS" mean the regular payments described in Paragraph 2.4(b) as increased and pursuant to Paragraph 2.4(c) and 2.8, but will not include the Excess Research Costs.

1.36 "RESEARCH TARGET PROFILE" means the scientific criteria specified by the Joint Research Committee to be fulfilled for a Compound to be met prior to designation of the Compound as a Development Candidate and prior to the initiation of IND-enabling toxicology, pharmacology and pharmacokinetic studies, including the methods for testing Compounds to determine whether the Profile is met. The Research Target Profile for the [*] are attached as Exhibit D.

1.37 "SHARED COMPOUND" means a Development Candidate which ZENECA proposes and ISIS accepts to develop and commercialize on a shared basis pursuant to Paragraph 3.5.

1.38 "SUBLICENSEE" means any Third Party (including a distributor) who is given the right to market and sell a Collaboration Product. A Third Party who is given only the right to sell a Collaboration Product (such as a wholesaler) will not be considered a Sublicensee. It is recognized and agreed that distributors appointed by ZENECA whose sole function is to purchase and resell Collaboration Product are not sublicensees for the purpose of this definition.

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1.39 "TARGETS" means specific individual molecular targets either initially or from time-to-time, collectively the Initial Targets, Cancer-Related Targets, and Non-Cancer-Related Targets. When an Active Target Program for a Target terminates, that Target will cease to be a Target and will thereafter become an Abandoned Target. Targets will include the Initial Targets plus any other Targets added or substituted pursuant to Paragraph 2.8 hereof, with any Abandoned Target when abandoned. Research relating to the Targets includes the elaboration of necessary cellular, biochemical and molecular-biological approaches (i.e., the development of the knowledge not already available to the two partners, the development and setting up of relevant assays) towards the inhibition of the expression of the proteinic target molecules by Antisense Technology as well as the conception, design, synthesis and development of therapeutic entities, including the characterization of their biophysical and pharmacokinetic properties.

1.40 [*].

1.41 "THIRD PARTY" means any party other than ISIS and its Affiliates or ZENECA and its Affiliates and Sublicensees.

1.42 "THIRD PARTY SUPPLIER" means any person or entity other than a party to this Agreement, its Affiliates, and/or its respective employees from whom ZENECA purchases commercial quantities of Bulk Drug Substance.

1.43 "ZENECA FIELD OF USE" means [*].

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EXHIBIT B
COLLABORATION RESEARCH PLAN

[*]

ENTIRE EXHIBIT REDACTED.

* CONFIDENTIAL TREATMENT REQUESTED

EXHIBIT C
JOINT RESEARCH COMMITTEE COMPOSITION

[*]

ENTIRE EXHIBIT REDACTED.

* CONFIDENTIAL TREATMENT REQUESTED

EXHIBIT D
RESEARCH TARGET PROFILE FOR THE INITIAL TARGETS

[*]

ENTIRE EXHIBIT REDACTED.

* CONFIDENTIAL TREATMENT REQUESTED

EXHIBIT E
TECHNICAL MILESTONE CRITERIA

[*]

ENTIRE EXHIBIT REDACTED.

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EXHIBIT F
MANUFACTURING SPECIFICATIONS

Typical Specifications for a Uniform Phosphorothioate Active Pharmaceutical Ingredient

IDENTITY:	
ES-MS	[*]
Sequencing by MALDI-TOF MS	[*]
Functionality	[*]
IMPURITY PROFILES: (AT LEAST TWO):	
P-NMR	[*]
Capillary Gel Electrophoresis	[*]
Reversed-phase HPLC	[*]
Anion Exchange HPLC	[*]
ASSAY: (AT LEAST ONE)	
Oligonucleotide Content by uV	[*]
Full-length Oligonucleotide by uV X CGE Impurity Profile	[*]
IMPURITIES:	
Organic Volatiles by Capillary GC	[*]
ACS Heavy Metals by ICP-MS	[*]
QUALITY:	
Endotoxins, USP	[*]
Bioburden, USP	[*]
OTHER:	
Sodium content	[*]
pH of 1% solution	[*]
Moisture Content (KF or GC)	[*]

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EXHIBIT G-1
ISIS LICENSES

CONTRACT	FIELD	PATENTS	PAYMENT OBLIGATIONS
CHEMISTRY			
Cross License Agreement (and amendments) with Novartis Pharma AG	[*]	[*]	In consideration for the reciprocal license, [*]; however, a royalty of [*] of sublicensee's net sales of each product in countries where the incorporation of the modifications into such product, or sale of such product would infringe an issued and valid Novartis patent
GENES			
Genzyme Molecular Oncology License Agreement	[*]	[*]	[*] of net sales of all licensed products

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EXHIBIT G-2
ISIS LICENSES

CONTRACT	FIELD	PATENTS	PAYMENT OBLIGATIONS
CHEMISTRY			
Ajinomoto License Agreement	[*]	[*]	[*] of net sales (gross invoice price to any third party, less only accepted returns from Isis's or Isis' sublicensee's customer, breakage, etc). Any transaction between Isis and any Isis sublicense shall not be included in net sales
PNA Group License Agreement	[*]	[*]	[*] royalty payable to PNA Group of net sales revenues and a [*] royalty of sublicensing revenue (not to be less than [*] of the sublicensee's net sales revenues) on sale of products covered by patents
Centre National De La Recherche Scientifique (CNRS) License Agreement	[*]	[*]	[*] of the billed sales price on products using patented technology
The Research Foundation of State University of New York License Agreement	[*]	[*]	[*] royalty of the net sales revenue derived by Isis or affiliates or sublicensees from the sale of products
Vical License Agreement	[*]	[*]	[*] royalty on the net sales revenues for patented products sold by Isis and [*] royalty of net sales revenues for patented products sold by Isis' sublicensees

CONTRACT	FIELD	PATENTS	PAYMENT OBLIGATIONS
Gen-Probe Assets Purchase Agreement	[*]	[*]	Total royalty payment of [*] on net sales revenues ([*]) received by Isis from the territories in which the issued patents subsists (i.e. United States and its territories, Australia, Canada, Israel and Japan) or on net sales revenues received by Isis from product made in the territories in which the issued patents subsists (i.e. United States and its territories, Australia, Canada, Israel and Japan)
McGill University Research and License Agreement	[*]	[*]	[*] royalty on Isis net sales revenue for any chirally pure oligonucleotide therapeutic or diagnostic product or reagent developed, manufactured or sold by Isis and [*] of all sublicensing revenues received from unrelated third parties

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EXHIBIT G-3
ISIS LICENSES

USE/PROCESS/MANUFACTURING

University Technologies International Inc. License Agreement	[*]	[*]	[*] of adjusted gross revenue on products sold as linker derivatized support matrices for oligonucleotide synthesis, [*] of adjusted gross revenue on products sold as nucleoside reagents with Q-linker or alternate linkers governed by patents, [*] of adjusted gross revenue on all other products with the exception of the therapeutic drug candidate
Applied Biosystems, Inc License Agreement	[*]	[*]	[*] of ABI published list price for a gram of the same or equivalent licensed reagent then being marketed by ABI
Perseptive Biosystems, Inc. License Agreement	[*]	[*]	Royalty free license to manufacture, have manufactured and use for its own use in house and for its own purposes and to incorporate as a raw material into its own products for its own use, the use of others or for sale, but not to sell licensed products, and to use licensed product
National Technical Information Service (NTIS) License Agreement	[*]	[*]	[*] royalty payable to NTIS on net sales revenues received by Isis from sales within the United States and its territories.

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EXHIBIT H
GMO TERM SHEET

ISIS REVISED PROPOSAL FOR NON-EXCLUSIVE LICENSE

November 12, 1998

Licensee:	Isis Pharmaceuticals, Inc. ("Isis")
Licensor:	Genzyme Corporation ("Genzyme")
Field:	Oligonucleotide Inhibition of [*] gene expression.
Patent rights:	The patent rights include any issued patents or patent applications owned by or assigned to Genzyme or licensed to Genzyme that would cover the discovery, development or commercialization of oligonucleotide inhibiting [*] gene expression. The patent rights specifically include without limitation patents or patent applications claiming priority to [*] including patents that issue on such patent applications and improvements, reissues, reexaminations, renewals, extensions, divisions, continuations, and continuations-in-part and foreign counterparts of such patents and patent applications.
License Grant:	Genzyme grants a non-exclusive, worldwide, royalty-bearing sublicense under the Patent Rights to discover, develop, make, have made, use, import and export, offer for sale, and sell Licensed Products for use in the Field (including the right to develop, make and use the Licensed Methods in the Field). Genzyme will also grant to Isis the right to sublicense, but only to the extent necessary to allow development and commercialization of an [*] antisense inhibitor as a drug. Any such sublicense will survive any termination of the Isis License if the sublicensee agrees to be bound by its terms. A Licensed Product shall mean a compound, the discovery, development, manufacture, use or sale of which would, but for the licenses granted hereunder, infringe a valid claim of an issued patent, the Patent Rights or a Licensed Method.

	A Licensed Method shall mean a method of use that is covered by an issued valid and unexpired claim of the patent rights.	
Up-front Payment:	$_____ within 30 days of signing	
Milestone Payments for the first Licensed Product :	[*]	$_____
	[*]	$_____
	[*]	$_____
	[*]	$_____
	[*]	$_____
	All milestone payments will be increased by ___% if commercialization of the Licensed Product would, except for the License Grant, otherwise infringe claims of issued US patent(s).	
Royalties:	___% on Net Sales of Licensed Products in territories where commercialization of the Licensed Product would, except for the License Grant, infringe a claim of a valid issued patent in the territory of sale. or: ___% on Net Sales of Licensed Products in territories where a Licensed Method was used to derive the Licensed Product, and where valid patent(s) with valid claim(s) covering the Licensed Method are in force.	
Credits/stacking	The upfront payment and milestone payments will not be creditable against royalties.	
Favored Licensee Status:	Genzyme agrees that if additional non-exclusive sublicenses are granted to third parties in the Field that ISIS will have the option to change the terms of the ISIS-Genzyme agreement to match those of the sublicensing agreement with the third party.	

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