UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE
SECURITIES EXCHANGE ACT OF 1934
FOR THE FISCAL YEAR ENDED DECEMBER 31, 1996
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)
619-931-9200
(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 $383,786,000 as of January 31, 1997.*

The number of shares of common stock outstanding as of January 31, 1997 was 26,235,805.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Registrant's definitive Proxy Statement which will be filed on or before April 21, 1997 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on June 6, 1997 is incorporated by reference into Part III of this Report.

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* Excludes 2,435,114 shares of common stock held by directors and officers and stockholders whose beneficial ownership exceeds ten percent of the shares outstanding at January 31, 1997. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

THIS FORM 10-K CONTAINS FORWARD-LOOKING STATEMENTS REGARDING THE COMPANY'S BUSINESS AND PRODUCTS AND THEIR PROJECTED PROSPECTS OR QUALITIES. SUCH STATEMENTS ARE SUBJECT TO CERTAIN RISKS AND UNCERTAINTIES, PARTICULARLY THOSE 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 PROJECTED IN THIS FORM 10-K. FACTORS THAT COULD CAUSE OR CONTRIBUTE TO SUCH DIFFERENCES INCLUDE, BUT ARE NOT LIMITED TO, THOSE DISCUSSED IN THIS FORM 10-K INCLUDING, WITHOUT LIMITATION, 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. ("Isis" or the "Company") is a leader in the discovery and development of novel drugs based upon antisense technology. Antisense technology enables the rapid design of novel drug candidates that have the potential to be safer and more effective than traditional drugs. The Company combines antisense technology with its core expertise in molecular and cellular biology and medicinal chemistry to develop drug candidates targeting a wide variety of diseases, including infectious and inflammatory diseases, and cancer. To date, Isis has advanced five antisense compounds into clinical trials and one additional antisense compound into preclinical development. In addition, through its medicinal chemistry expertise, Isis has developed a proprietary combinatorial drug discovery program to create and rapidly screen diverse libraries of small molecule compounds as potential drug candidates. Isis has one compound in clinical trials that was discovered through its combinatorial drug discovery program. The Company believes that its antisense and combinatorial drug discovery programs address complementary therapeutic opportunities and are synergistic due to their common reliance on Isis' significant medicinal chemistry capabilities.

Isis' drug discovery programs have produced the following compounds currently in clinical trials:

ISIS 2922 ("fomivirsen") is in Phase III clinical trials as an antiviral agent to treat CMV retinitis in AIDS patients. Isis is developing ISIS 2922 in North America, Europe, South America and Australia.

ISIS 2302 is in Phase II clinical trials for five indications as an inhibitor of intercellular adhesion molecule-1 ("ICAM-1") to treat renal transplant rejection, rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriasis. ICAM-1 is a protein involved in numerous inflammatory disorders and diseases. ISIS 2302 is a component of Isis' cell adhesion collaboration with Boehringer Ingelheim International GmbH ("Boehringer Ingelheim").

ISIS 3521/CGP 64128A is in Phase I clinical trials for treatment of solid tumors. ISIS 3521/CGP 64128A is targeted at protein kinase C ("PKC")-a, a member of a family of signal transduction proteins involved in the regulation of cell growth and thought to be involved in a variety of inflammatory diseases and cancer. ISIS 3521/CGP 64128A is a compound that is part of Isis' collaboration with Novartis Pharma AG (formed from the merger of Ciba-Geigy and Sandoz) ("Novartis"), the development of which is being conducted by Isis.

ISIS 5132/CGP 69846A is in Phase I clinical trials for treatment of solid tumors. ISIS 5132/CGP 69846A inhibits C-raf kinase, a molecular target associated with both normal and abnormal cell growth. ISIS 5132/CGP 69846A is a compound that is part of Isis' collaboration with Novartis, the development of which is being conducted by Isis.

ISIS 5320 is in Phase I clinical trials for the treatment of human immunodeficiency virus (HIV). This compound has been shown in vitro to inhibit virus-to-cell and cell-to-cell transmission of HIV. It has exhibited anti-viral activity against a variety of clinical HIV-1 and HIV-2 strains, including a panel of drug resistant isolates.

The Company's drug discovery programs have also generated one additional compound in preclinical development, an antisense compound which has shown potent activity in animal models of Ha-ras, a cancer-related target.

Isis is also conducting a number of target-based research programs using its antisense and combinatorial drug discovery technologies. Isis' antisense research programs focus on molecular targets associated with infectious and inflammatory diseases and cancer as well as on the development of second-and third-generation compounds with altered and improved therapeutic properties. The Company's combinatorial drug discovery program is primarily focused on identifying compounds targeting important RNA protein interactions including those involved in viral and bacterial infections and in inhibiting the production or function of cell adhesion molecules.

Isis has leveraged its technology through supportive corporate collaborations which augment the Company's financial resources, add complementary technology strength and establish valuable development and commercialization relationships. As a result, Isis has been able, and expects to continue, to pursue more aggressively drug discovery and development activities than otherwise might be possible. Isis has retained substantial commercial participation to all of its potential products, including those funded by corporate collaborators.

Isis has made significant progress in expanding its collaborations with pharmaceutical partners. In February 1996, Isis and Novartis signed an agreement to expand their collaboration with respect to the development of ISIS 5132/CGP 69846A and to broaden their collaboration further to include the development of ISIS 3521/CGP 64128A, research to discover additional therapeutic compounds targeting the PKC family of signal transduction proteins and the c-raf kinase family of signal transduction proteins and development of any such compounds. In 1995, Isis consummated a substantial collaboration with Boehringer Ingelheim which joins the clinical development and research programs of both companies in the field of cell adhesion. This partnership combines Boehringer Ingelheim's significant expertise in cell adhesion biology and its small molecule and monoclonal antibody-based drug discovery efforts with Isis' antisense and combinatorial drug discovery programs. The collaboration will use these multiple drug discovery technologies to identify compounds to treat a variety of inflammatory diseases and conditions. As part of the collaboration, Boehringer Ingelheim made an equity investment in Isis and will make additional equity investments upon the achievement of certain development milestones. In 1996, Isis met the first milestone, triggering a $10 million equity investment by Boehringer Ingelheim. Isis and Boehringer Ingelheim will share equally the costs associated with the development of these compounds and the operating profits associated with these compounds, if any. Isis also has a corporate collaboration with the Chemo Sero Therapeutic Research Institute ("Kaketsuken") to identify antisense compounds to treat hepatitis C virus.

Isis has focused significant efforts on developing cost-effective, large scale Good Manufacturing Practices ("GMP") manufacturing capability for antisense compounds. Isis currently manufactures antisense compounds to meet its research and clinical needs. Significant progress has been made by Isis in reducing the cost of manufacturing antisense compounds. Isis believes that, with reasonably anticipated benefits from increases in scale, the Company can manufacture such compounds at commercially competitive costs. The Company is actively preparing for a manufacturing pre-approval inspection by the U.S. Food and Drug Administration ("FDA"), which will follow the filing of the Company's first New Drug Application.

ISIS DRUG DISCOVERY AND DEVELOPMENT

Drug discovery is the process of creating chemical compounds having the appropriate attributes to produce desired therapeutic effects. Isis has founded both its antisense and its combinatorial drug discovery programs on its expertise in medicinal chemistry, RNA biochemistry and molecular and cellular biology. Isis has assembled a team of scientists skilled in these core disciplines to apply these technologies to both of its drug discovery platforms.

ANTISENSE DRUG DISCOVERY

Early efforts in antisense drug discovery have focused on answering basic questions regarding antisense-based therapeutics, including their stability, ability to be taken up by the target cells, efficacy and cost of manufacturing. In the eight years since its founding, Isis has made significant progress in understanding and using antisense technology and has established a leadership position in this field. Isis' antisense drug discovery programs are able to rapidly identify attractive lead drug candidates directed against numerous host and infectious disease targets. The Company's first-generation antisense compounds have demonstrated activity in numerous models of disease in animals. In addition, ISIS 2922, an antisense compound for the treatment of CMV-induced retinitis, has shown antiviral activity in humans and ISIS 2302, an antisense inhibitor of ICAM-1, has shown activity in patients with Crohn's disease. Next-generation chemical modifications of these compounds are demonstrating the ability to increase safety and potency and to alter other drug properties in ways that may be advantageous. Through the development of proprietary scale-up chemistries, Isis has also demonstrated the ability to manufacture antisense compounds in large scale and to substantially reduce the manufacturing cost.

Antisense drugs work at the genetic level to interrupt the process by which disease-causing proteins are produced. Proteins play a central role in virtually every aspect of human metabolism. Almost all human diseases are the result of inappropriate protein production or disordered protein performance. Traditional drugs are designed to interact with protein molecules throughout the body that support or cause diseases. Antisense drugs are designed to inhibit the production of disease-causing proteins and can be designed to treat a wide range of diseases including infectious, inflammatory and cardiovascular diseases and cancer. Antisense drugs have the potential to be more selective and, as a result, more effective and less toxic than traditional drugs.

The information necessary to produce proteins in cells is contained in genes. Specific genes contain information to produce specific proteins. The information required for the human body to produce all proteins is contained in the human genome and its collection of more than 100,000 genes. Genes are made up of DNA that contains information about when and how much of which protein to produce, depending upon what function is to be performed. The DNA molecule is a "double helix" -- a duplex of entwined strands. In each duplex, the building blocks of DNA, the nucleotides, are weakly 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 contained in the gene is copied from one strand of DNA into precursor messenger RNA ("mRNA") through a process called transcription. A particluar mRNA contains the information necessary to produce many copies of one particular protein. The precursor mRNA is then processed through a complex set of steps into mature mRNA and is transported 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 proteins.

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 acting at this stage in the disease-causing process to prevent the production of a disease-causing protein, antisense drugs have the potential to provide greater therapeutic benefit than traditional drugs which do not act until the disease-causing protein has already been produced.

Antisense drugs also have the potential to be much more selective and specific than traditional drugs, and therefore more effective. The design of antisense compounds also has the advantage of being less complex, more rapid and more efficient than traditional drug design directed at protein targets. Rational drug design usually begins by characterizing the three-dimensional structure of the protein target in order to design a prototype drug to interact with the target. Proteins, however, are complex molecules whose structure is difficult to predict. In contrast, antisense compounds are designed to bind to mRNA whose structures are more easily understood and predicted. Once the receptor sequence on the mRNA is identified, the three-dimensional structure of the receptor site can be defined, and the prototype antisense drugs can be designed.

COMBINATORIAL DRUG DISCOVERY

Isis has developed a novel combinatorial drug discovery capability that is complementary to its antisense drug discovery capability. The significant medicinal chemistry expertise of Isis and its collaborators supports the strong chemical underpinning of the program. Isis' combinatorial drug discovery program enables the Company to discover compounds with the potential to treat a wide range of diseases where the structure of the target may not be known or where the extreme specificity of antisense compounds may not be desirable, such as in designing antibacterial drugs that require a wide spectrum of activity to be attractive. The combinatorial drug discovery program is a significant factor in Isis' collaboration with Boehringer Ingelheim. See "--Collaborative Agreements--Boehringer Ingelheim."

The goal of combinatorial drug discovery is to create large, highly diverse libraries of chemical compounds which can be screened for biological activity against a wide variety of disease targets. The greater the chemical diversity (e.g., size, shape, charge, rigidity, etc.) that a combinatorial program can produce, the greater the probability of finding compounds with meaningful biological activity and, thus, potential therapeutic application. For decades, the pharmaceutical industry has relied on using natural product extracts or chemical banks to provide chemical compounds to screen for biological activity in pharmaceutical assays. These sources of compounds have inherent limitations both in terms of their current accessibility and their chemical diversity. In addition, when natural compound libraries evidence activity in assays, it frequently is extremely difficult to identify the active compound, and, when identified, such compound may be difficult to synthesize. The need for more efficient ways to access and screen chemical diversity has led the scientific community to look for alternatives to conventional chemical bank and natural product extract screening. Combinatorial drug discovery, which harnesses and exploits randomness and synthetically creates chemical diversity, offers unlimited quantities of potentially unique biologically active compounds and accelerates the identification of drug candidates.

Isis has focused its internal combinatorial screening program on drug resistant bacteria. There is a need for new classes of antimicrobial compounds that work by novel mechanisms. RNA/protein interactions represent novel mechanisms for small molecule drug discovery with the potential for a broad spectrum of activity. Contacts between RNA and protein are highly conserved and essential to the life cycles of bacteria. These contacts are often distinctly different or completely absent in humans. Novel chemical inhibitors of these evolutionarily conserved targets may have activity against drug resistant or newly emergent disease causing bacteria.

In collaboration with the Defense Advanced Research Projects Agency ("DARPA"), Isis is using comparative bacterial genome sequence analysis and bioinformatics methods to identify and prioritize essential conserved RNA/protein targets. The Company is approaching these targets with a combinatorial chemical technology that applies the principles of molecular evolution to drug discovery using small organic molecules. A large number of chemical shapes are created by assembling a defined number of chemical units in numerous permutations and then testing for a desired activity. Although the permutations are random, the choices of chemical units are rational and based upon computational methods that utilize information from small molecules and proteins that bind RNA as well as information from high throughput screening.

The program uses novel chemistries, proprietary to Isis, to create these compounds libraries. The libraries contain low molecular weight compounds that are structurally stable and may not require extensive modification to be useful drug candidates. The combinatorial libraries can be screened in solution which increases the breadth of pharmaceutical assays in which they can be evaluated. Isis uses fully automated instrumentation to synthesize many of its combinatorial libraries. The equipment has distinct advantages in speed and efficiency over other robotic instruments and thus significantly enhances the productivity of combinatorial library production.

The combinatorial drug discovery program has already yielded ISIS 5320, a compound in clinical development, that has shown promising biological activity against HIV. See "--Products Under Development--Infectious Disease--Human Immunodeficiency Virus."

PRODUCTS UNDER DEVELOPMENT

Isis' drug discovery programs use antisense and combinatorial drug discovery technologies to identify compounds to treat infectious and inflammatory diseases and cancer. The following table summarizes the disease indications and development status of, as well as Isis' commercial rights to, each product under development. There can be no assurance that any of the listed product candidates will progress beyond its current status or yield a commercially viable product. The Company also has a significant research program with the potential to yield additional development candidates in the future. See "--Research Programs."

TARGET	COMPOUND	DISEASE INDICATION	DEVELOPMENT STATUS(1)	COMMERCIAL RIGHTS
CLINICAL DEVELOPMENT				
CMV	ISIS 2922 ("fomivirsen")	Retinitis	Phase III	Isis
ICAM-1	ISIS 2302	Crohn's disease	Phase II	Isis/Boehringer
		Renal transplant rejection	Phase II	Ingelheim(2)
		Rheumatoid arthritis	Phase II	
		Ulcerative colitis	Phase II	
		Psoriasis	Phase II	
PKC-a,	ISIS 3521/ CGP 64128A	Cancer	Phase I	Novartis(3)
C-raf kinase	ISIS 5132/ CGP 69846A	Cancer	Phase I	Novartis(3)
HIV	ISIS 5320	AIDS	Phase I	Isis(4)
PRECLINICAL DEVELOPMENT				
Ha-ras	ISIS 2503	Cancer	IND candidate	Isis

(1) "IND candidate" indicates a compound for which IND-enabling toxicology and pharmacokinetic studies have been initiated and IND preparation has begun. There can be no assurance that drugs discovered by the Company will prove efficacious or will be commercially successful.

(2) Isis and Boehringer Ingelheim are co-developing ISIS 2302. Isis and Boehringer Ingelheim will split profits from this product equally if and when it is commercialized. See "--Collaborative Agreements--Boehringer Ingelheim."

(3) Isis and Novartis are co-developing ISIS 3521/CGP 64128A and ISIS 5132/CGP 69846A at Novartis' expense. Novartis will have world-wide rights to market these compounds, subject to a royalty to Isis, and Isis will have certain manufacturing rights. "--See Collaborative Agreements--Novartis."

(4) Preclinical development of ISIS 5320 was funded, in part, by the National Cancer Institute ("NCI").

INFECTIOUS DISEASES

Cytomegalovirus ("CMV"). CMV produces opportunistic infections in immuno-compromised patients, primarily those with AIDS. In the AIDS population, retinitis caused by CMV is the primary cause of blindness, occurring in 25% to 40% of patients during the course of their illness. There are approximately 220,000 active AIDS cases in the U.S., and the prevalence is growing by 5% to 15% each year. While the recent introduction of new anti-HIV drugs, particularly protease inhibitors, and combination treatment regimens may slow the deterioration of the immune system and prolong survival in HIV-infected individuals, the vast majority of the approximately one million HIV-infected individuals are, neverless, expected to ultimately progress to and through the advanced stages of AIDS where CMV retinitis generally occurs. These patients represent a significant pool of potential CMV retinitis cases. Currently available therapies for CMV retinitis have limitations and frequently result in viral resistance.

Isis has discovered an antisense compound, ISIS 2922 ("fomivirsen"), for the treatment of CMV-induced retinitis. ISIS 2922 entered clinical trials in December 1993. In the Phase I/II study, patients with advanced CMV retinitis, which had proven refractory to currently available drug therapies, were treated with intravitreal injections of ISIS 2922. Approximately two-thirds of the patients in the two middle dose groups showed positive clinical responses to the drug, and in most of these patients progress of the disease was halted within the first two weeks of treatment. Many of the disease remissions seen in the trial were of significant duration. ISIS 2922 was well tolerated at the doses tested. The Company believes that ISIS 2922 was the first antisense compound to demonstrate efficacy in humans in a multi-patient clinical trial.

The Phase III trials, which started in December 1994, are designed to include over 300 patients in four randomized study designs: one comparing immediate ISIS 2922 therapy with no therapy until disease progression; the second comparing ISIS 2922 treatment in combination with ganciclovir to ganciclovir alone; and the third and fourth studying different dosing regimens for ISIS 2922 in a patient population with advanced CMV retinitis which has proven refractory to current drug therapies. All four study designs will examine the time to disease progression, and are ongoing.

Isis has reported on data from an ongoing open-label uncontrolled trial of ISIS 2922 in patients with advanced CMV retinitis whose disease had progressed despite treatment with other CMV retinitis therapies. When treated with ISIS 2922, many patients achieved significant therapeutic utility, including extended progression free periods, some as long as 12-18 months, despite the advanced

stage of their CMV retinitis. While these results are not conclusive, they confirm the therapeutic benefit of ISIS 2922 and suggest an attractive clinical profile. There can be no assurance that ISIS 2922 will prove safe or effective at the current doses, or at any other doses, or that ISIS 2922 will be approved by the FDA.

Currently approved drugs for CMV retinitis are ganciclovir, foscarnet and cidofovir. Foscarnet and cidofovir are avaliable in intravenous dosing forms only. Ganciclovir is available in intravenous, oral and intraocular implant dosing forms. Intravenous induction and maintenance therapy with ganciclovir and foscarnet require daily administrations using permanent indwelling catheters, and each drug is associated with significant systemic toxicities. Oral ganciclovir is approved for prophylaxis and maintenance therapy, but is less efficacious than IV ganciclovir and still carries significant systemic side-effects. The ganciclovir intraocular implant provides local sustained release of drug over five to eight months, but treatment is associated with impaired vision for two to four weeks after implantation in most patients, and a significant incidence of retinal detachment, 12-18% after the first implant and over 30% following a second or third implant, that can itself permanently destroy vision. Cidofovir is administered less frequently, weekly for induction therapy and every two weeks for maintenance therapy, but is associated with significant toxicities, particularly to the kidneys, that require cidofovir to be administered in conjunction with other drugs and strict safety measures over a period of approximately twelve hours to ameliorate or prevent toxicities.

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 fomivirsen. Local therapy with ISIS 2922 could provide therapeutic effects without systemic side effects or the need for intravenous treatments, reserving systemic anti-CMV therapy in combination with ISIS 2922 for the patients who acquire symptoms of systemic disease (approximately one-third of the patients within one year after diagnosis of CMV retinitis).

Isis is pursuing its CMV drug development program, including the development of ISIS 2922 in North America, Europe, Australia and South America. U.S. Patent No. 5442049, issued August 15, 1995, covers the composition of matter for ISIS 2922 and U.S. Patent No. 5595978, issued January 21, 1997, covers methods of treatment of CMV retinitis using ISIS 2922.

Human Immunodeficiency Virus ("HIV"). Approximately one million people in the United States are estimated to be infected with HIV. HIV-infected individuals ultimately develop AIDS which causes severe suppression of the immune system, leaving the body susceptible to opportunistic infections and cancer. Since the discovery of HIV as the causative agent of AIDS, the main treatment strategy has been to keep the virus from proliferating in infected individuals. The majority of the therapeutic agents developed to date to treat HIV act either by inhibiting viral enzymes, such as reverse transcriptase or protease, or by arresting expression of viral genes or gene products.

Through its combinatorial drug discovery program, Isis has discovered a compound to prevent replication of HIV. ISIS 5320 is a potent and specific inhibitor of HIV infection as demonstrated in a panel of in vitro arrays. ISIS 5320 has also shown significant antiviral activity in vitro at low concentrations and is effective against HIV 1 and 2, drug-resistant strains of HIV and all clinical isolates tested. Furthermore, ISIS 5320 has demonstrated dose-dependent anti-viral activity in an NIH-approved animal model, the SCID-hu thy/liv mouse. ISIS 5320 may also be suitable for administration in combination with currently available HIV therapies, which could then be administered at lower and less toxic doses. The Company filed an IND for ISIS 5320 in December 1996 and initiated Phase I clinical studies in January 1997. U.S. Patent No. 5523389, issued June 4, 1996, covers the composition of matter for ISIS 5320.

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 injured tissues, disruptions of normal inflammatory processes often lead to inflammatory diseases. These inflammatory disorders 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 and organ transplant rejection. The cause of inflammation at the molecular level is becoming better understood. Isis' inflammation drug discovery and development program focuses on cell adhesion molecules.

Cell Adhesion Molecules. Cell adhesion molecules make up a large family of related proteins and represent targets for treating inflammatory diseases. During periods of hyperimmune activity, certain members of this protein family are expressed on the outside of the endothelial cells which line the blood vessels of the body. These adhesion molecules act as anchors for various types of immune cells circulating in the blood. Once these cells are anchored to the endothelial cells by adhesion molecules, they can migrate between the endothelial cells, leave the blood vessels and travel into tissues and organs where they propagate the inflammatory response. Left unchecked, these processes can result in acute and chronic tissue damage and disease. Cell adhesion molecules have been associated with many inflammatory disorders, coagulation disorders, bacterial infections and the spread of cancer in the body. Currently used anti-inflammatory and immunosuppressive agents 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. Inhibitors of cell adhesion molecules may prevent the migration of immune cells from the vasculature into tissue and therefore modify the disease process with a more acceptable toxicity profile than currently available therapies.

Isis has focused on a number of targets in its cell adhesion molecule program. The Company is specifically focused on the intercellular adhesion molecule ("ICAM") family and in particular, ICAM-1. Isis' focus on ICAM-1 allows the Company to target both chronic and acute inflammatory conditions since, unlike other adhesion molecules, ICAM-1 facilitates the migration of immune cells involved in both acute and chronic inflammation. Over-expression of ICAM-1 is specifically implicated in a wide variety of inflammatory disorders, such as rheumatoid arthritis, asthma, psoriasis, organ transplant rejection and inflammatory bowel disease. 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 or conditions.

In 1995, Isis and Boehringer Ingelheim agreed to combine their 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 assay technology, with Isis' antisense and combinatorial drug discovery programs. The collaboration will use these multiple drug discovery technologies to identify compounds that inhibit the disease-related functions of cell adhesion molecules. See "--Collaborative Agreements--Boehringer Ingelheim."

ISIS 2302, the Company's lead compound in its cell adhesion program, selectively inhibits ICAM-1 gene expression in vitro. Isis has conducted extensive preclinical studies with an antisense inhibitor of murine ICAM-1, that as closely as possible matches the characteristics of ISIS 2302, an inhibitor of human ICAM-1. Compounds from Isis' ICAM-1 program have demonstrated highly potent therapeutic activity in animal models of cardiac transplant rejection, arthritis, tumor metastasis (malignant melanoma), inflammatory bowel disease, as well as in other models of induced inflammation.

Phase I testing of ISIS 2302 was completed in the first quarter of 1995. In the Phase I study, which was conducted on healthy volunteers, the compound was well tolerated at all doses including those expected to have therapeutic activity. Based on activity observed in a broad range of animal models of inflammatory disease, the Company has initiated Phase II trials in five disease indications -- rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis and prevention of renal transplant rejection -- to provide initial safety and efficacy data for these indications. The studies involve 20 to 40 patients each and, in general, are randomized and placebo-controlled. The choice of indications for subsequent development of ISIS 2302, if any, will be made based on results from these studies.

In the Phase II study of patients with Crohn's disease, ISIS 2302 demonstrated safety and efficacy. In this randomized, double-blinded, placebo-controlled study, 47% of patients treated with ISIS 2302 were in disease remission versus 0% in the placebo group at the end of the one-month treatment phase. The mean duration of remission in responding patients was prolonged, lasting almost five months following a single course of treatment. The results of this study were supported by a statistically significant (p=0.0001) lowering of the corticosteroid requirements in the ISIS 2302 treated group, as well as by favorable trends in Endoscopic Index of Severity (EIS) and Inflammatory Bowel Disease Questionaire (IBDQ) assessments. Based on the results of this study, Isis and its partner, Boehringer Ingelheim, have decided to proceed with full-scale development of ISIS 2302 in Crohn's disease.

Isis is pursuing its cell adhesion drug development program with Boehringer Ingelheim, including the development of ISIS 2302, in North America and Europe. U.S. Patents No. 5514788, issued May 7, 1996, and No. 5591623, issued January 7, 1997, cover the composition of matter for ISIS 2302.

CANCER

Much of Isis' work in the area of cancer is focused on 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. Until recently, tools have not existed to determine the functional differences among the isotypes within a multigene family since traditional drug molecules are insufficiently specific to inhibit one isotype within a family without affecting the function of the other related isotypes. In contrast, antisense drug discovery technology exploits the differences among the isotypes at the mRNA level to design isotype-specific inhibitors. Isis has focused its cancer drug discovery program on multigene families due to growing evidence that certain isotypes might be differentially involved in abnormal (rather than normal) cell differentiation or proliferation and that selective inhibition of a single isotype may result in less toxicity than general inhibition of a family of proteins significantly involved in the daily functions of the body. Much of Isis' work has focused on multigene families in the signal transduction pathway. In addition, Isis focuses on targets, such as oncogenes, more traditionally associated with cancer.

Signal Transduction Molecules. Information about the environment surrounding a cell in the body is transferred into cells by specific cellular and extracellular proteins through cellular membranes by a process called "signal transduction." The cell uses a large number of different but, in many cases, related proteins to carry out signal transduction processes. Disordered regulation of these signal transduction proteins is thought to be involved in numerous proliferative disorders, including cancer.

PKC. Isis has an antisense compound in Phase I clinical development which inhibits the production of a particular isotype of PKC. PKC is a key enzyme in signal transduction, and isotypes of PKC are associated with the growth of certain types of cancer. Isis has shown that its PKC compounds can specifically inhibit the production of single isotypes of PKC without inhibiting the production of other isotypes. Isis has recently shown in animals that an antisense compound targeting one specific

isotype, PKC-a, can specifically eradicate PKC-a mRNA expression with no effect on the mRNA levels of other PKC isotypes, thus confirming the antisense mechanism of action in vivo.

Isis' most advanced compound from its PKC discovery program is ISIS 3521/CGP 64128A, a potent and highly specific antisense inhibitor of the PKC-a isotype. In nude mouse xenografts of various human tumor types, ISIS 3521/CGP 64128A exhibits potent anti-tumor activity at doses well below those that result in side effects. The Company filed an IND for ISIS 3521/CGP 64128A in December 1995 and initiated Phase I clinical studies in the first quarter of 1996. Completion of the Phase I studies is expected in the second quarter of 1997. The drug has been well tolerated in the 40 patients treated to date and there have been no unanticipated toxicities. Phase II clinical trials are planned to start in the third quarter of 1997 in the U.S., Canada and Europe.

In February 1996, Isis and Novartis signed a definitive agreement to broaden their collaboration further to include the development of ISIS 3521/CGP 64128A, research to discover additional therapeutic compounds targeting the PKC family of signal transduction proteins and development of any such compounds. See "--Collaborative Agreements--Novartis."

C-raf Kinase. In its collaboration with Novartis, Isis is developing another antisense compound, ISIS 5132/CGP 69846A, which inhibits C-raf kinase, another molecular target involved in cell signaling. C-raf is a member of a multigene family and is associated with abnormal cell growth. Isis and Novartis have shown that ISIS 5132/CGP 69846A selectively inhibits C-raf without inhibiting the production of other members of the multigene family. Studies of three different human tumor cell lines in cell culture have demonstrated that ISIS 5132/CGP 69846A inhibits expression of its target in a specific and concentration dependent manner. Studies in a nude mice xenograft model have demonstrated that ISIS 5132/CGP 69846A reduces the growth of a variety of solid tumor types at doses well below those that result in side effects. In March 1996, Isis commenced Phase I clinical studies with ISIS 5132/CGP 69846A. Phase I trials are expected to be completed in the second quarter of 1997. The drug has been well tolerated and the Company plans to begin Phase II studies in the third quarter of 1997 in the U.S., Canada and Europe. See "--Collaborative Agreements--Novartis." U.S. Patent No. 5563255, issued October 8, 1996, covers the composition of matter for ISIS 5132.

Ras. Isis' drug discovery program in the cancer area focuses on the discovery of antisense compounds to inhibit the expression of the two different ras proteins, Ha-ras and Ki-ras. Although the exact role of ras in human malignant disease is still being studied, these proteins appear to be involved in the process by which tumor cells respond to growth factors and other extracellular stimuli. The altered responses of tumor cells cause these cells to grow and proliferate in a "deregulated" or malignant manner. Mutations of ras genes and over-expression of ras proteins have been implicated in a variety of human cancers, including solid tumor types such as colon, bladder, breast, kidney, lung and liver as well as certain hematopoietic tumors. Isis is evaluating a number of ras antisense compounds in animal efficacy models and has shown inhibition of the growth of a variety of human tumors in a number of animal models at doses well below those that result in side effects. In addition, the Company is applying its second- and third-generation chemistries to create highly potent and specific new ras antisense drugs. Isis has compounds targeting both Ha-ras and Ki-ras in preclinical development, including ISIS 2503, an inhibitor of the Ha-ras, for which the Company plans to file an IND in 1997.

RESEARCH PROGRAMS

Isis combines its core technology programs in medicinal chemistry, RNA biochemistry and molecular and cellular biology with molecular target-focused drug discovery efforts to create future drug candidates for its product development pipeline. The goal of Isis' target-based research programs is to identify antisense and combinatorial drug candidates to treat diseases for which there are substantial markets and the potential for significant improvement over existing therapies. In addition, Isis' research programs focus on identifying second-generation compounds to serve as backup compounds to its products in development and development candidates. Isis' combinatorial drug discovery program

is currently focused on cell adhesion molecules in connection with its collaboration with Boehringer Ingelheim and on identifying broad-spectrum anti-infective agents with a focus on important drug-resistant infections. See "--Collaborative Agreements--Boehringer Ingelheim."

Isis' core technology programs can support multiple target-based antisense research programs without significant incremental expense, allowing Isis to explore efficiently numerous disease targets and identify the most attractive lead compounds to advance to preclinical development. Isis is currently pursuing antisense and combinatorial drug discovery programs focused on various antiviral and antibacterial targets, inflammatory disease targets, and other key molecular targets that might play critical roles in cancer.

COLLABORATIVE AGREEMENTS

Isis' strategy is to balance corporate collaborations and equity-based financings to augment the Company's financial resources, reduce risk and retain commercial rights to its pipeline of products in development. Through collaborative partnerships with major pharmaceutical companies, Isis broadens its target programs, obtains funding for existing programs, accesses complementary technologies and gains significant development and commercialization expertise. Isis intends to continue to pursue this strategy.

NOVARTIS

In January 1995, Isis and Ciba-Geigy Limited ("Ciba") agreed to extend their collaborative research program for an additional three years. In September 1995, Isis and Ciba signed a letter of intent to broaden the collaboration. After making an $8.5 million equity investment in Isis at the commencement of the collaboration in September 1990, Ciba purchased an additional 129,000 shares of common stock for approximately $1 million in January 1993 and an additional 200,000 shares of common stock at $15 per share for $3 million in June 1995. Ciba purchased 700,000 shares of common stock in the Company's public offering completed in October 1995 at $10 per share. In 1996, Ciba agreed to merge with Sandoz forming a new company known as Novartis. As of December 31, 1996, Novartis beneficially owned approximately 9% of the Company's outstanding common stock.

Beginning in September 1995, the research collaboration has focused on PKC and C-raf kinase (the "Novartis Targets"). In this collaboration, Isis is committing substantial resources to discover and investigate antisense compounds that inhibit the Novartis targets. Novartis is providing financial support for the research relating to these targets at Isis and is committing substantial resources of its own to the application of medicinal chemistry to antisense drugs, the development of large scale manufacturing processes, and the provision of antisense compounds for extended research evaluation. Isis has granted Novartis the option, exercisable prior to clinical development, to obtain an exclusive license in all countries to develop, manufacture, use and market any compounds arising out of the collaboration directed to the Novartis Targets (the "Novartis Compounds"). In the event that Novartis exercises its option to obtain an exclusive license for any Novartis Compound, Isis and Novartis will co-develop the Novartis Compound at Novartis' expense. Isis will receive certain milestone payments as the first two Novartis Compounds for each target progress through development. For any Novartis Compound so licensed, Isis and Novartis will be jointly responsible for the clinical development of, and obtaining all regulatory approvals related to, the Novartis Compound in all countries other than Japan where Novartis will have sole responsibility for development. With certain exceptions, in the event that Novartis fails to exercise its option with respect to any Novartis Compound, it forfeits all rights to such Novartis Compound. Novartis has exercised its option with respect to ISIS 5132/CGP 69846A and ISIS 3521/CGP 64128A. In connection with these exercises, Isis, at Novartis' expense, is conducting the preclinical and clinical development of these compounds. See "--Products Under Development--Cancer--Signal Transduction Molecules--PKC" and "--C-Raf Kinase."

Isis will receive royalties on sales of each Novartis Compound, including ISIS 5132/CGP 69846A and ISIS 3521/CGP 64128A, as to which Novartis exercises its option. Novartis has the exclusive world-wide rights to market Novartis Compounds. Any commercial manufacturing of ISIS 5132/CGP 69846A and ISIS 3521/CGP 64128A is expected to be done by Isis in return for an additional royalty on sales of such compounds. Any commercial manufacturing of additional Novartis Compounds is to be determined based on cost, quality and supply factors.

Either Novartis or, with certain exceptions, Isis may terminate the collaborative research program beginning in September 1998, and under certain circumstances Novartis may terminate the research program earlier. There can be no assurance that ISIS 5132/CGP 69846A, ISIS 3521/CGP 64128A or any other Novartis Compound will be successfully developed under the agreement with Novartis, or that Isis will receive the royalties contemplated by such agreement.

BOEHRINGER INGELHEIM

In July 1995, Isis and Boehringer Ingelheim formed a collaboration to combine the clinical development and research programs of both companies in the field of cell adhesion. Isis will contribute its expertise in antisense and combinatorial drug discovery and Boehringer Ingelheim will contribute its ongoing program in cell adhesion biology and small molecule library screening capabilities. Both companies will provide ongoing funding for the combined research and development program. The research program will be managed by a joint representation Research Management Committee. Research will be conducted at both Isis and Boehringer Ingelheim. Compounds arising out of the research program are candidates for joint development, with development decisions made by a joint representation Development Coordination Committee. A joint representation Executive Committee will manage the overall collaboration. A party choosing not to fund its share of the development expenses for a compound will receive royalties on any future sales of such compounds.

In July 1995, Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28.5 million in cash plus certain license rights. Of the $28.5 million, $21.3 million has been accounted for as equity and $7.2 million has been accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. In December 1996, Boehringer Ingelheim made a $10 million milestone payment by purchasing an additional 409,000 shares of common stock. Of the $10 million, $6 million has been accounted for as equity and $4 million has been recorded as deferred revenue. As of December 31, 1996, Boehringer Ingelheim owned approximately 9% of the outstanding common stock of the Company. See Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations--Liquidity and Capital Resources." In addition to funding one-half of the research and development budgets, Boehringer Ingelheim will make additional equity investments in Isis when certain development milestones are met and will also provide a $40 million line of credit to Isis which is available under certain circumstances. As of December 31, 1996, outstanding borrowings under this line of credit totaled $16.2 million.

The partnership includes: enlimomab, Boehringer Ingelheim's murine monoclonal antibody targeting ICAM-1, which is currently in Phase III clinical trials; ISIS 2302, an antisense inhibitor of ICAM-1; and multiple other preclinical and research compounds targeting other adhesion molecules. Upon commercialization, Isis and Boehringer Ingelheim will share equally in the operating profits associated with all future products of the collaboration. Boehringer Ingelheim will market the first two drugs arising out of the collaboration. The parties will mutually agree on commercialization responsibilities for subsequent products, if any. In addition, Isis will receive a royalty with respect to worldwide sales of enlimomab, if any.

ISIS 2302, an antisense inhibitor of ICAM-1 expression discovered by Isis, is in Phase II clinical trials for five indications. See "--Products Under Development--Inflammatory Diseases--Cell Adhesion Molecules." This compound is a part of Isis' collaboration with Boehringer Ingelheim and is

being developed by an Isis-led project team. There can be no assurance that ISIS 2302, enlimomab or any other compound arising out of Boehringer Ingelheim's collaboration with Isis will be successfully developed or that Isis will receive the revenue contemplated by such agreement. 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.

EISAI

In December 1990, Isis entered into a collaborative research program with Eisai which concluded in 1993 when a compound arising out of the collaboration, ISIS 2922, was accepted by Eisai for development. Isis and Eisai proceeded to co-develop ISIS 2922 in Europe and the United States. Isis conducted the clinical development program, and Eisai paid half the costs of this development. In August 1996, Isis reacquired full ownership of ISIS 2922 in exchange for a royalty on future sales of ISIS 2922. The Company will be responsible for funding all future development costs for this compound. ISIS 2922 is currently in Phase III clinical trials. See "--Products Under Development--Infectious Diseases--Cytomegalovirus." There can be no assurance that ISIS 2922 will be successfully developed.

KAKETSUKEN

Isis entered into a collaborative research agreement for a three-year research program with Kaketsuken in July 1992. Kaketsuken was collaborating in this program with Mochida Pharmaceutical Co., Ltd. ("Mochida"). In July 1995, Mochida terminated its participation in the collaboration. For the first three years of the collaboration, Isis committed significant resources to discover and investigate antisense compounds active against hepatitis C virus, and Kaketsuken provided financial support for the necessary research at Isis. Isis has granted Kaketsuken the option to obtain an exclusive license in Japan to use or sell any compounds discovered in the research program or, under certain circumstances, during the next four years. Isis has also granted Kaketsuken the option to obtain an exclusive license to make or have made any licensed compound. Kaketsuken has agreed to develop, sell and commercially exploit any licensed compound. In the event that Kaketsuken fails to exercise its option with respect to any compound, it forfeits all rights to such compound.

Isis has received initial research and option fees and will receive additional option and license fees and royalties on sales of any products licensed to Kaketsuken. Isis has the right to develop and market worldwide all products discovered in the research program, except for licensed compounds which it may not develop or market in Japan.

Kaketsuken has the right to terminate the collaboration. There can be no assurance that any compound will be successfully developed under the agreement with Kaketsuken or that Isis will receive the additional payments or royalties contemplated by such agreement.

MANUFACTURING

Chemically modified oligonucleotides, such as those used in the Company's research and development programs, have generally been expensive and difficult to produce except in small quantities. As a result, the Company has focused on the development of improved manufacturing capacity as an important factor for its long-term success and has dedicated significant resources to achieving this objective. To date, through the development of several proprietary scale-up chemistries, Isis has substantially reduced its cost of producing oligonucleotide compounds and substantially increased its capacity to manufacture such compounds. The Company has both internal programs and external collaborations with various industry vendors to further advance its manufacturing capability.

The production of chemically-modified oligonucleotides, like the chemical synthesis used in the production of traditional pharmaceuticals, does not involve any fermentation processes or living cells and therefore entails lower manufacturing costs than processes that utilize fermentation. The Company is applying its expertise in organic chemistry and chemical synthesis to the development of proprietary manufacturing processes to increase capacity and reduce the costs of producing oligonucleotides. Because all oligonucleotide compounds are composed of variants of the same nucleotide building blocks and are produced using the same types of equipment, the Company believes that the capabilities and know-how that it develops in manufacturing one oligonucleotide drug product will be equally applicable to the manufacture of future products. The Company has sufficient manufacturing capacity to meet current research and development needs. The Company believes that it has or will be able to develop or acquire sufficient supply capacity to meet its anticipated needs and that, with reasonably anticipated benefits from increases in scale, will be able to manufacture antisense compounds at commercially competitive costs.

PATENTS, TRADE SECRETS AND LICENSES

Proprietary protection for the Company's product candidates, processes and know-how is important to Isis' business. Thus, the Company plans to aggressively prosecute and defend its patents and proprietary technology. The Company's policy is to file patent applications to protect technology, inventions and improvements that are considered important to the development of its business. The Company also relies upon trade secrets, know-how, continuing technological innovation and licensing opportunities to develop and maintain its competitive position.

As of January 31, 1997, Isis held 51 issued U.S. patents, including composition-of-matter patents covering ISIS 5320, ISIS 5132 and ISIS 2302, and had received notices of allowance for an additional 33 patents. The Company has also filed more than 250 patent applications involving chemistry, processes, biological insights and specific target-oriented compositions of matter with the U.S. Patent and Trademark Office and, in some cases, with the corresponding offices in other countries, including members of the European Patent Convention, Canada, Japan, South Korea and Australia. Isis currently has 35 issued foreign patents.

The Company has filed applications for patents relating to chemical compositions for therapeutic and, in some cases, diagnostic use in the treatment of certain diseases. The Company believes that these patents, if granted and upheld, will be a key to the Company's success. The Company has also filed patent applications regarding methods of preparation and use of certain novel nucleoside monomers, oligonucleotide analogs, linkages for oligonucleotide analogs and key intermediates in the synthesis of oligonucleotide analogs. Composition of matter patents have been filed which define oligonucleotide sequences and structures that are relevant to many of the RNA targets the Company is currently pursuing. In addition, the Company has filed patent applications resulting from novel discoveries made by its employees relating to nucleic acid structure and biochemistry, which it believes will be broadly applicable and important to the discovery, development and commercialization of oligonucleotide-based drugs. The Company has also filed patent applications regarding novel discoveries arising out of its combinatorial drug discovery program, including applications on methods of making libraries and identifying active compounds; on novel chemical constructions and methods of building combinatorial libraries; and on the combinatorial libraries. As lead compounds are identified, the Company also files patent applications on those compounds.

The patent positions of pharmaceutical, biopharmaceutical and biotechnology firms, including Isis, are generally uncertain and involve complex legal and factual questions. Consequently, even though Isis is currently prosecuting its patent applications with the U.S. and foreign patent offices, the Company does not know whether any of its 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. Since patent applications in the United States are maintained in

secrecy until patents issue, and since publication of discoveries in the scientific or patent literature tend to lag behind actual discoveries by several months, Isis cannot be certain that it was the first creator of inventions covered by pending patent applications or that it was the first to file patent applications for such inventions.

There can be no assurance that the Company's patents or those of its competitors, if issued, would be held valid by a court of competent jurisdiction. Moreover, to determine priority of invention, the Company may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office or opposition proceedings before an equivalent foreign agency with respect to any of its existing patents or patent applications or any future patents or patent applications, which could result in substantial cost to the Company.

Competitors or potential competitors have filed applications for, or have received patents and may obtain additional patents and proprietary rights relating to, compounds or processes competitive with those of the Company. Accordingly, there can be no assurance that the Company's patent applications will result in patents being issued or that if issued the patents will afford protection against competitors with similar technology; nor can there be any assurance that others will not obtain patents that the Company would need to license or circumvent. The Company is aware of three issued patents owned by the U.S. government regarding the use of phosphorothioates, a specific type of oligonucleotide analog, in the treatment of certain human diseases. The Company is using phosphorothioates in a number of its programs in a manner which may be covered by these patents. The U.S. government granted a license to the Company in September 1995. The patents have, in part, been licensed to other companies on a co-exclusive basis.

The Company also relies upon unpatented trade secrets, and there can be no assurance that others will not independently develop substantially equivalent proprietary information and techniques or otherwise gain access to the Company's trade secrets or disclose such technology, or that the Company can meaningfully protect its right to unpatented trade secrets.

Isis requires its employees, consultants, members of the Scientific Advisory Board, outside scientific collaborators and sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with the Company. These agreements provide that all confidential information developed or made known to the individual during the course of the individual's relationship with Isis is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual shall be the exclusive property of the Company. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for the Company's trade secrets in the event of unauthorized use or disclosure of such information.

GOVERNMENT REGULATION

The Company's 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 the Company or its licensees or marketing partners in their respective efforts to secure necessary

governmental approvals, which could delay or preclude the Company or its licensees or marketing partners from marketing their products.

As an initial step in the FDA regulatory approval process, preclinical studies are typically conducted in animals to identify potential safety problems. For certain diseases, animal models exist which are believed to be predictive of human efficacy. For such diseases, a drug candidate is tested in such animal model. The results of the studies are submitted to the FDA as a part of an IND application, which is filed to comply with FDA regulations prior to beginning human clinical testing. For other diseases for which no appropriately predictive animal model exists, no such results can be filed. For several of the Company's drug candidates, no appropriately predictive animal model exists. As a result, no in vivo evidence of efficacy would be available until such a compound progresses to human clinical trials.

Clinical trials are typically conducted in three sequential phases, although the phases may overlap. In Phase I, which frequently begins with the initial introduction of the drug into healthy human subjects prior to introduction into patients, the compound will be tested for safety and dosage tolerance. Phase II typically involves studies in a somewhat larger patient population to identify possible adverse effects and safety risks, to begin gathering preliminary efficacy data and to investigate potential dose sizes and schedules. Phase III trials are undertaken to further evaluate clinical efficacy and to further test for safety within an expanded patient population. Each trial is conducted in accordance with certain standards under protocols that detail the objectives of the study, the parameters to be used to monitor safety and the efficacy criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND. Further, each clinical study must be evaluated by an independent Institutional Review Board ("IRB") at the institution at which the study will be conducted. The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution.

Data from preclinical testing and clinical trials are submitted to the FDA in a New Drug Application ("NDA") for marketing approval. Preparing an NDA involves considerable data collection, verification, analysis and expense, and there can be no assurance that any approval will be granted on a timely basis, if at all. The approval process is affected by a number of factors, including the severity of the disease, the availability of alternative treatments and the risks and benefits demonstrated in clinical trials. The FDA may deny an NDA if applicable regulatory criteria are not satisfied, require additional testing or information or require post-marketing testing and surveillance to monitor the safety of the Company's products. Quality control and manufacturing procedures conforming to GMP are conditions for clinical studies and NDA approval. In complying with standards set forth in these regulations, manufacturers must continue to expend time, money and effort in the area of production and quality control to ensure full technical compliance. After FDA approval for the initial indications, further clinical trials would be necessary to gain approval for the use of a product for any additional indications. Approvals may be withdrawn if compliance with labeling and GMP regulatory standards is not maintained or if unexpected safety problems occur following initial marketing.

The Company has filed INDs and commenced clinical trials with respect to six compounds: ISIS 2922, ISIS 2105, ISIS 2302, ISIS 3521/CGP 64128A, ISIS 5132/CGP 69846A and ISIS 5320. ISIS 2922 is currently in Phase III clinical trials, which commenced in December 1994, for the treatment of CMV-induced retinitis in AIDS patients. In August 1995, the Company began Phase II clinical trials of ISIS 2302 to treat renal transplant rejection and subsequently began Phase II trials for Crohn's disease, rheumatoid arthritis, psoriasis and ulcerative colitis. In January 1996, the Company began Phase I clinical trials of ISIS 3521/CGP 64128A to treat solid tumors. In March 1996, the Company began Phase I clinical trials of ISIS 5132/CGP 69846A which also targets solid tumors. In January 1997, the Company began Phase I clinical trials of ISIS 5320 to treat HIV.

Under Title 35 of the United States Code as amended by the General Agreement on Tariffs and Trade implementing the Uruguay Round Agreement Act of 1994 ("GATT"), patents that issue from patent applications filed prior to June 8, 1995, will enjoy a 17-year period of enforceability as measured from the date of patent issue while those that issue from applications filed on or after June 8, 1995 will enjoy a 20-year period of enforceability as measured from the date the patent application was filed or the first claimed priority date, whichever is earlier. Patents that issue from applications filed on or after June 8, 1995, may be extended under the term extension provisions of GATT for a period of up to five years to compensate for any period of enforceability lost due to interference proceedings, government secrecy orders or appeals to the Board of Patent Appeals or the Federal Circuit. Under the Drug Price Competition and Patent Restoration Act of 1984, including amendments implemented under GATT ("the Patent Term Restoration Act"), the period of enforceability of a first or basic product patent or use patent covering a drug may be extended for up to five years to compensate the patent holder for the time required for FDA regulatory review of the product. This law also establishes a period of time following FDA approval of certain drug applications during which the FDA may not accept or approve applications for similar or identical drugs from other sponsors. Any extension under the Patent Term Restoration Act and any extension under GATT are cumulative. There can be no assurance that the Company will be able to take advantage of either the patent term extension or marketing exclusivity provisions of this law.

In addition to regulations enforced by the FDA, the Company is 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. The Company believes that it is in compliance in all material respects with applicable laws and regulations.

COMPETITION

For many of their applications, 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 the Company's existing or potential competitors have substantially greater financial, technical and human resources than the Company and may be better equipped to develop, manufacture and market products. In addition, many of these companies have extensive experience in preclinical testing and human clinical trials. These companies may develop and introduce products and processes competitive with or superior to those of the Company. 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.

The Company's products under development address an array of markets. The Company's competition will be determined in part by the potential indications for which the Company's compounds are developed and ultimately approved by regulatory authorities. For certain of the Company's potential products, an important factor in competition may be the timing of market introduction of its or competitive products. Accordingly, the relative speed with which Isis can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market is expected to be an important competitive factor. The Company expects 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 treatment methods not based on oligonucleotide-based technology for those indications for which the Company is developing compounds could render such compounds non-competitive or obsolete. Furthermore, because of the fundamental differences between oligonucleotide and other technologies, there may be applications for which the products of one

technology are superior to those of another. Isis is aware of several companies with late-stage compounds in development for indications targeted by the Company.

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

EMPLOYEES

As of January 31, 1997, Isis employed 287 individuals, of whom 112 hold advanced degrees. A significant number of the Company's management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Isis believes that it has been highly successful in attracting skilled and experienced scientific personnel; however, competition for such personnel is intensifying. The Company's employees are not covered by collective bargaining agreements, and management considers relations with its employees to be good.

EXECUTIVE OFFICERS

The executive officers of the Company and their ages as of February 28, 1997 are as follows:

STANLEY T. CROOKE, M.D., PH.D.... 51
Chairman of the Board and Chief Executive Officer

Stanley T. Crooke, M.D., Ph. D., was a founder of the Company and has been its Chief Executive Officer and a director since January 1989 and Chairman of the Board since February 1991. He served as President 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 SIBIA Neurosciences, Inc. and GeneMedicine, Inc., both biotechnology companies, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. Dr. Crooke is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

DANIEL L. KISNER, M.D.... 50
President and Chief Operating Officer

Daniel L. Kisner, M.D., has served as a director of the Company since March 1991, Chief Operating Officer since February 1993 and President since May 1994. He was Executive Vice President of the Company from March 1991 until May 1994. From December 1988 until March 1991, he was a Division Vice President of Pharmaceutical Development for Abbott Laboratories, a pharmaceutical company. He is also a director of Anesta Corporation, a drug delivery company.

B. LYNNE PARSHALL.... 41
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. 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.

RISK FACTORS

The following risk factors should be considered carefully in addition to the other information contained in this Report.

UNCERTAINTY ASSOCIATED WITH CLINICAL TRIALS

Subject to compliance with FDA regulations, Isis plans to undertake extensive and costly clinical testing to demonstrate optimal dose, safety and efficacy for its compounds in development. There can be no assurance that the Company will be able to submit an IND application to the FDA to obtain authorization for human clinical testing of any of its compounds currently in research or preclinical development. The Company or the FDA may suspend clinical trials at any time if the subjects or patients participating in such trials are being exposed to unacceptable health risks. Further, there can be no assurance that human clinical testing will show any current or future product candidate to be safe or efficacious or that any such product will be approved by the FDA for any indication.

The rate of completion of the Company's clinical trials is dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays, which could have a material adverse effect on the Company.

There also can be no assurance that any authorized clinical testing will be completed successfully within any specified time period, if at all, with respect to any of the Company's current or future product candidates. There can be no assurance that the Company will not encounter problems in its clinical trials which would cause the Company or the FDA to delay or suspend the trials.

NO ASSURANCE OF REGULATORY APPROVAL

The production and marketing of the Company's products and its ongoing research and development activities are subject to regulation by numerous federal, state and local governmental authorities in the United States. Similar regulatory authorities exist in other countries where the Company intends to test and market its products. Prior to marketing, any drug developed by the Company must undergo an extensive regulatory approval process. In addition, each clinical study is conducted under the auspices of an independent IRB. The IRB will consider, among other things. ethical factors, the safety of human subjects and patients and the possible liability of the host institution.

The regulatory process, which includes preclinical and clinical testing of each compound to establish its safety and efficacy, can take many years and require the expenditure of substantial resources. Data obtained from preclinical and clinical activities are susceptible to varying interpretations which could delay, limit or prevent FDA regulatory approval. In addition, delays or rejections may be encountered based upon changes in FDA policy for drug approval during the period of product development and FDA regulatory review of each submitted new drug application. Similar delays may also be encountered in foreign countries. There can be no assurance that, even after such time and expenditures, regulatory approval will be obtained for any drugs developed by the Company. Moreover, if regulatory approval of a drug is granted, such approval may entail limitations on the indicated uses for which it may be marketed. Further, even if such regulatory approval is obtained, a marketed drug, its manufacturer and its manufacturing facilities are subject to continual review and periodic inspections, and later discovery of previously unknown problems with a product, manufacturer or facility may result in restrictions on such product or manufacturers, including a withdrawal of the product from the market. Failure to comply with the applicable regulatory requirements can, among other things, result in fines, suspensions of regulatory approvals, product recalls, operating restrictions and criminal prosecution. Further, additional government regulation may be established which could prevent or delay regulatory approval of the Company's products.

DEPENDENCE ON COLLABORATIVE PARTNERS

Isis has relied on certain established pharmaceutical companies interested in its various technology platforms to fund a portion of its research and development expenses. The Company has entered into research and development agreements with these collaborative partners whereby the partners provide capital in exchange for certain technology, product, manufacturing and/or marketing rights related to the targets of the collaborative research. Under certain of these agreements, the collaborative partner will have the responsibility for conducting preclinical testing and human clinical trials and for preparing and filing the submission for regulatory approval of the product candidate with the FDA and certain other regulatory agencies in specified territories, and in certain circumstances, worldwide. In addition, certain of these agreements provide for Isis to receive royalties or other revenues based on sales of products developed primarily by the corporate partners. Should any collaborative partner fail to develop or commercialize successfully any product to which it has rights, or any of the partner's products to which Isis has rights, the Company's business may be adversely affected. While Isis believes that its collaborative partners will have sufficient economic motivations to continue their funding, there can be no assurance that any of these collaboration will be continued or result in successfully commercialized products. A failure of a corporate partner to continue funding any particluar program could delay or halt the development or commercialization of any products arising out of such program. In addition, there can be no assurance that the collaborative partners will not be pursuing alternative technologies or developing alternative compounds either on their own or in collaboration with others, including the Company's competitors, as a means for developing treatments for the diseases targeted by these collaborative programs. Isis also may rely on additional collaborative arrangements to develop and commercialize its products in the future. There can be no assurance that the Company will be able to negotiate acceptable collaborative arrangements in the future, or that such collaborative arrangements will be successful.

EARLY STAGE OF DEVELOPMENT; TECHNOLOGICAL UNCERTAINTY

Isis is at an early stage of development. To date, most of the Company's resources have been dedicated to applying molecular biology and medicinal chemistry to the research and development of potential pharmaceutical products based upon antisense technology. The Company has five compounds in clinical trials and has other compounds in preclinical development. Conduct of clinical trials in humans is necessary to determine whether or not a compound will be an attractive or effective drug. 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. For example, the Company is attempting to develop products, including ISIS 2922, for certain diseases for which no appropriately predictive animal efficacy model currently exists. As a result, drug candidates for these diseases must progress at least to Phase II human clinical trials before Isis will have evidence of in vivo efficacy for such compounds. There can be no assurance that drugs discovered by the Company will prove efficacious or will be commercially successful. Products, if any, resulting from Isis' research and development programs are not expected to be commercially available for a number of years.

CONTINUING OPERATING LOSSES

Isis has incurred net losses since its inception in January 1989. At December 31, 1996, the Company's accumulated deficit was approximately $123 million. Such losses have resulted principally from costs incurred in the Company's research and development programs and from general and administrative costs associated with the Company's growth and operations. These costs have exceeded the Company's revenues, which to date have been generated primarily from collaborative arrangements, interest income and research grants. No revenues have been generated from product sales. The Company expects to incur additional operating losses over the next several years and expects losses to increase as the Company's preclinical testing and clinical trial efforts expand. The Company's ability to achieve profitability is dependent in part on obtaining regulatory approvals for its products,

entering into agreements for product development and commercialization and developing the capacity to manufacture and sell its products successfully. There can be no assurance that the Company will obtain required regulatory approvals, successfully develop, commercialize, manufacture and market its products or ever achieve profitability.

FUTURE CAPITAL NEEDS; UNCERTAINTY OF ADDITIONAL FUNDING

The Company anticipates that its existing capital resources will be adequate to satisfy its current capital requirements for at least the next two years. The Company's future capital requirements will depend on many factors, including continued scientific progress in its research, drug discovery and development programs, the magnitude of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments; changes in the existing collaborative relationships and the ability of the Company to establish and maintain additional collaborative arrangements; and the cost of manufacturing scale-up and effective commercialization activities and arrangements. To the extent that existing resources are insufficient to fund the Company's activities, additional funds may be raised, including through public or private financings. There can be no assurance that additional financing will be available, or, if available, that it will be available on acceptable terms. If additional funds are raised by issuing equity securities, further dilution to then existing stockholders may result. If adequate funds are not available, the Company may be required to significantly curtail one or more of its research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others that may require the Company to relinquish rights to certain of its technologies, product candidates or products.

POSSIBLE OBSOLESCENCE DUE TO TECHNOLOGICAL CHANGE; COMPETITION

Certain companies, both private and publicly traded, are conducting research and development activities on oligonucleotide technology and products. The Company believes that the investigation of the potential of oligonucleotide therapeutics will continue and may accelerate as the techniques which permit oligonucleotide drug design and development are more widely understood. Competitors of the Company 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. There can be no assurance that the Company's competitors will not succeed in developing oligonucleotide therapeutics or other novel therapeutic compounds that are more effective than any which have been or are being developed by the Company or which would render Isis' technology and products obsolete and non-competitive prior to the Company recovering research, development or commercialization expenses.

Many of the Company's competitors have substantially greater financial, technical and human resources than the Company. In addition, many of these competitors have significantly greater experience than the Company in undertaking preclinical testing and human clinical trials of new pharmaceutical products and obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, the Company's competitors may succeed in obtaining FDA approval for products earlier than the Company. Furthermore, if the Company is permitted to commence commercial sales of products, it will also be competing with respect to manufacturing efficiency and marketing capabilities, areas in which it has limited or no experience.

DEPENDENCE ON PATENTS AND PROPRIETARY RIGHTS

The Company's success will depend in part on its ability to obtain patent protection for its products both in the United States and in other countries. The Company intends to file applications as appropriate for patents covering both its products and processes. As of January 31, 1997, Isis had been issued 51 U.S. patents and had filed more than 250 patent applications in the United States and foreign

counterparts of certain of these applications in many countries. There can be no assurance that patents will issue from any of these applications. Since patent applications in the United States are maintained in secrecy until patents issue, and since publication of discoveries in the scientific or patent literature tends to lag behind actual discoveries by several months, Isis cannot be certain that it was the first creator of inventions covered by pending patent applications or that it was the first to file patent applications for such inventions. Further, there can be no assurance that the claims allowed under any issued patents will be sufficiently broad to protect the Company's proprietary position in its technology. In addition, there can be no assurance that any patents issued to the Company will not be challenged, invalidated or circumvented, or that the rights granted thereunder will provide competitive advantages to the Company.

The commercial success of the Company will also depend in part on neither infringing patents issued to competitors nor breaching the technology licenses upon which the Company's products might be based. While the Company is aware of patent applications and patents belonging to competitors, it is uncertain whether these will require the Company to alter its products or processes, pay licensing fees or cease certain activities. The Company is aware of certain patents and patent applications owned by the U.S. government regarding the use of phosphorothioates, a specific type of oligonucleotide analog, in the treatment of certain human diseases. The Company is using phosphorothioates in a manner which may be covered by these patents or patent applications. The U.S. government granted a license to the Company in September 1995. This patent application has in part been licensed to certain other companies on a co-exclusive basis. Although the Company has been offered a license to this technology and is in the process of negotiating the terms of such license, there can be no assurance that the Company will obtain this license. Further, there can be no assurance that the Company will be able to obtain a license to other technology that it may require or that, if obtainable, such technology can be licensed at reasonable cost. Failure by the Company to obtain a license to any technology that it may require to commercialize its products may have a material adverse impact on the Company. Litigation, which could result in substantial cost to the Company, may also be necessary to enforce any patents issued to the Company and/or to determine the scope and validity of others' proprietary rights in court or administrative proceedings. In addition, to determine the priority of inventions, the Company may have 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 its existing patents or patent applications or any future patents or applications, which could result in substantial cost to the Company. Further, the Company may have to participate at substantial cost in International Trade Commission proceedings to abate importation of goods which would compete unfairly with products of Isis.

Under Title 35 of the United States Code as amended by GATT, patents that issue from patent applications filed prior to June 8, 1995, will enjoy a 17-year period of enforceability as measured from the date of patent issue while those that issue from applications filed on or after June 8, 1995 will enjoy a 20-year period of enforceability as measured from the date the patent application was filed or the first claimed priority date, whichever is earlier. Patents that issue from applications filed on or after June 8, 1995, may be extended under the term extension provisions of GATT for a period up to five years to compensate for any period of enforceability lost due to interference proceedings, government secrecy orders or appeals to the Board of Patent Appeals or the Federal Circuit. Under the Patent Term Restoration Act, the period of enforceability of a first or basic product patent or sue patent covering a drug may be extended for up to five years to compensate the patent holder for the time required for FDA regulatory review of the product. This law also establishes a period of time following FDA approval of certain drug applications during which the FDA may not accept or approve applications for similar or identical drugs from other sponsors. Any extension under the Patent Term Restoration Act and any extension under GATT are cumulative. There can be no assurance that the Company will be able to take advantage of such patent term extensions or marketing exclusivity provisions of these laws. While the Company cannot predict the effect that such changes will have on its business, the adoption of such changes could have a material adverse effect on the Company's ability to protect its proprietary information and sustain the commercial viability of its products. Furthermore, the possibility of

shorter terms of patent protection, combined with the lengthy FDA review process and possibility of extensive delays in such process, could effectively further reduce the term during which a marketed product could be protected by patents.

Isis also relies on trade secrets and proprietary know-how which it seeks to protect, in part, by confidentiality agreements with its corporate partners, collaborators, employees and consultants. There can be no assurance that these agreements will not be breached, that the Company would have adequate remedies for any breach, or that the Company's trade secrets will not otherwise become known or be independently discovered by competitors.

LIMITED MANUFACTURING EXPERIENCE

The Company's ability to operate profitably will depend in part on its ability to manufacture its products at a competitive cost. To successfully establish commercial manufacturing capability, Isis must improve its manufacturing processes and must reduce its 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 commercial scale. There can be no assurance that such molecules can be manufactured by the Company or any other party at a cost or in quantities necessary to make commercially viable products.

ABSENCE OF SALES AND MARKETING CAPABILITIES

The Company has no experience in sales, marketing or distribution. To market any of its products directly, the Company must develop a marketing and sales force with technical expertise and with supporting distribution capability. There can be no assurance that the Company will be able to build such a sales force at all, or at a reasonable cost, or that its direct sales and marketing efforts will be successful. As with any new product, there can be no assurance that any of the Company's products, if approved by the FDA, will achieve market acceptance in lieu of existing treatments.

UNCERTAINTIES ASSOCIATED WITH THIRD-PARTY REIMBURSEMENT

The Company's ability to commercialize its products, if any, depends in part on the extent to which reimbursement for the cost of such products and related treatments will be available from government health administration authorities, private health coverage insurers and other organizations. There can be no assurance that adequate third-party coverage will be available for the Company to obtain satisfactory price levels for third-party payor reimbursements. Government and other third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement for new therapeutic products. If adequate coverage and reimbursement levels are not provided by government and third-party payors for uses of the Company's potential products, the market acceptance of these products would be adversely affected.

DEPENDENCE ON KEY EMPLOYEES AND CONSULTANTS

The Company is highly dependent on the principal members of its management and scientific staff, the loss of whose services might impede the achievement of development objectives. Furthermore, recruiting and retaining qualified scientific personnel to perform research and development work in the future will also be critical to the Company's success. Although the Company believes it will be successful in attracting and retaining skilled and experienced scientific personnel, there can be no assurance that the Company will be able to attract and retain such personnel on acceptable terms given the competition among numerous pharmaceutical and health care companies, universities and non-profit research institutions for experienced scientists.

Isis' anticipated growth and expansion into areas and activities requiring additional expertise, such as clinical testing, regulatory affairs, production and marketing, are expected to place increased demands on the Company's resources. These demands are expected to require the addition of new management personnel and the development of additional expertise by existing management personnel. The failure to acquire such services or to develop such expertise could have a material adverse effect on the prospects for the Company's success.

PRODUCT LIABILITY AND POTENTIAL LIMITS OF INSURANCE COVERAGE

The use of drugs in clinical trials and, if approved, the sale of such drugs may expose the Company to liability claims resulting from the use of such products. These claims might be made directly by consumers or by sellers or distributors of the Company's products. Isis has obtained limited product liability insurance coverage. However, such coverage is becoming increasingly expensive, and there can be no assurance that the Company will be able to maintain such insurance at a reasonable cost or in sufficient amounts to protect the Company against losses due to liability that could have a material adverse effect on the Company.

USE OF HAZARDOUS MATERIALS

The Company's research and development activities involve the controlled use of hazardous materials, chemicals, viruses and various radioactive compounds. Although the Company believes that its safety procedures for handling and disposing of such materials comply with the standards prescribed by local, state and federal regulations, the risk of accidental contamination or injury from these materials cannot be completely eliminated. In the event of such an accident, the Company could be held liable for any damages that result and any such liability could have a material adverse effect on the financial condition of the Company. Although the Company believes that it is in compliance in all material respects with applicable environmental laws and regulations and currently does not expect to make material capital expenditures for environmental control facilities in the near term, there can be no assurance that it will not be required to incur significant costs to comply with environmental laws and regulations in the future, or that the operations, business or assets of the Company will not be materially adversely affected by current or future environmental laws or regulations.

ANTI-TAKEOVER PROVISIONS

The Company's Certificate of Incorporation provides for classified terms for the members of the Board of Directors and includes a provision (the "Fair Price Provision") that requires the approval of the holders of at least 66-2/3% of the Company's voting stock as a condition to a merger or certain other business transactions with, or proposed by, a holder of 15% or more of the Company's voting stock, except in cases where certain Directors approve the transaction or certain minimum price criteria and other procedural requirements are met. The Company's Certificate of Incorporation also requires that any action required or permitted to be taken by stockholders of the Company must be effected at a duly called annual or special meeting of stockholders and may not be effected by any consent in writing. In addition, special meetings of the stockholders of the Company may be called only by the Board of Directors, the Chairman of the Board or the President of the Company or by any person or persons holding shares representing at least 10% of the outstanding common stock. The classified board, Fair Price Provision and other charter 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 may deem to be in their best interests. In addition, the Board of Directors has the authority to fix the rights and preferences of and issue shares of Preferred Stock, which may have the effect of delaying or preventing a change in control of the Company without action by the stockholders.

VOLATILITY OF STOCK PRICE

The market price of the common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. Factors such as fluctuation in the Company's operating results, announcements of technological innovations or new commercial therapeutic products by the Company or its competitors, governmental regulation, regulatory approval, development in patent or other proprietary rights, public concern as to the safety of drugs developed by the Company and general market conditions may have a significant effect on the market price of the common stock.

ABSENCE OF DIVIDENDS

The Company has never paid any cash dividends and does not anticipate paying cash dividends in the foreseeable future.

ITEM 2. PROPERTIES

Isis occupies approximately 86,000 square feet of laboratory and office space in four buildings located in Carlsbad, California. These buildings are owned by the Company and, as of December 31, 1996, secure approximately $6.8 million in indebtedness of the Company. Isis has leased an additional 46,000 square feet of laboratory and office space which will be available for occupancy in March, 1997. The Company believes that its facilities will be adequate to meet its needs through 1998.

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

The common stock (NASDAQ symbol "ISIP") is traded publicly through the NASDAQ National Market System. 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 System. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW
1995		
First Quarter	$ 8.63	$ 3.63
Second Quarter	$ 14.63	$ 6.00
Third Quarter	$ 15.25	$ 11.25
Fourth Quarter	$ 14.25	$ 9.38
1996		
First Quarter	$ 15.13	$ 10.88
Second Quarter	$ 24.75	$ 10.38
Third Quarter	$ 19.50	$ 11.75
Fourth Quarter	$ 20.50	$ 15.38

As of January 31, 1997, there were approximately 1,347 stockholders of record of the common stock. The Company has never paid dividends and does not anticipate paying any dividends in the foreseeable future. Under the terms of certain term loans, the Company will be 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,				
	1996	1995	1994	1993	1992
STATEMENT OF OPERATIONS DATA:					
Research and development revenues	$ 22,572	$ 12,966	$ 10,088	$ 10,654	$ 8,727
Research and development expenses	45,653	33,175	26,468	25,604	23,120
Net loss	(26,521)	(23,712)	(18,181)	(19,062)	(19,510)
Net loss per share	(1.04)	(1.10)	(0.93)	(1.22)	(1.51)
Shares used in computing net loss per share	25,585	21,514	19,542	15,685	12,892

	DECEMBER 31,				
	1996	1995	1994	1993	1992
BALANCE SHEET DATA:					
Cash, cash equivalents and short-term investments	$ 77,624	$ 77,407	$ 43,440	$ 54,034	$ 36,354
Working capital	56,300	60,040	33,679	44,076	29,518
Total assets	101,305	99,569	66,643	78,814	55,474
Long-term debt and capital lease obligations, less current portion	19,864	4,714	9,295	8,847	6,674
Accumulated deficit	(123,067)	(96,546)	(72,834)	(54,653)	(35,591)
Stockholders' equity	58,385	75,850	46,019	58,459	39,849

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

Since its inception in January 1989, the Company has devoted substantially all of its resources to its research, drug discovery and drug development programs. The Company has been unprofitable since its inception and expects to incur additional operating losses for the next several years. The Company has entered into collaborative research and development agreements with pharmaceutical companies that generate revenue to augment the level of research and development activity and to offset portions of its research and development costs. See Item 1, "Business--Collaborative Agreements." To date, the Company has not received any significant revenue from the sale of products.

RESULTS OF OPERATIONS

Years Ended December 31, 1996 and December 31, 1995

The Company had contract revenues from collaborative research and development agreements of $22.6 million for 1996 compared with $13.0 million in 1995, an increase of 74%. The revenue increase was due in part to revenue received under agreements with Novartis to conduct the preclinical and clinical development of drug candidates identified through the collaborative research program between Novartis and Isis. Additional revenue from a collaborative agreement with Boehringer Ingelheim, formed in 1995, also contributed to the increase. The Company also had interest income totaling $4.0 million for the year ended December 31, 1996 versus $3.0 million in 1995. This increase was due to higher cash and short-term investment balances.

Research and development expenses increased 38% to $45.7 million for 1996 from $33.2 million in 1995. This increase was primarily attributable to the Company's growing preclinical and clinical development activities. In 1995, the Company recorded a charge of $733,000 to research and development expense relating to its repurchase of rights in PerIsis I Development Corporation ("Perisis I"). The Company expects its development expenses will continue to increase as its current preclinical and clinical activities advance and additional preclinical and clinical studies are undertaken.

General and administrative expenses increased 15% to $6.2 million for 1996 from $5.4 million in 1995. This increase was principally due to expanded business development and investor relations activities and to the costs associated with hiring additional administrative personnel in support of the Company's increasing research and development efforts. The Company expects that its general and administrative expenses will continue to increase in the future in support of its expanding operations.

During 1996, the Company recorded a net loss of $26.5 million, or $1.04 per share, compared with $23.7 million, or $1.10 per share, for 1995. The change in net loss per share reflected the increase in the weighted average number of shares outstanding due to the sale of common stock in the second half of 1995 offset by the increase in the net loss for 1996. The Company expects that its operating losses will increase for several more years as its activities grow, and may fluctuate from quarter to quarter as a result of differences in the timing and composition of revenue earned and expenses incurred.

At December 31, 1996, the Company had available net operating loss carryforwards of approximately $119.1 million and $7.7 million for federal and state income tax purposes, respectively. The Company's research credit carryforwards were approximately $4.5 million and $1.8 million for federal and state income tax purposes, respectively. Because of "change of ownership" provisions of the Tax Reform Act of 1986, the Company's net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods. The Company believes that such limitation will not have a material adverse impact on the benefits that may arise out of its net operating loss and tax credit carryforwards, but there can be no assurance that additional limitations arising from any future changes in ownership will not have a material adverse impact on the Company.

The Company believes that inflation and changing prices have not had a material effect on its ongoing operations to date.

Years Ended December 31, 1995, and December 31, 1994

The Company had $13.0 million of contract revenues from collaborative research agreements in 1995 and $10.1 million in 1994, an increase of 29%. The increase was primarily due to revenue received under collaborative agreements with Novartis and Boehringer Ingelheim. The Company also had interest income of $3.0 million in 1995 and $2.3 million in 1994. The increase in interest income in 1995 was due to higher investment balances.

Research and development expenses increased 25% to $33.2 million in 1995 from $26.5 million in 1994. This increase was attributable to expanded preclinical and clinical research and development activities.

General and administrative expenses decreased 10% to $5.4 million in 1995 from $6.0 million in 1994, reflecting lower recruiting and relocation expenses.

The Company recorded net losses of $23.7 million in 1995 and $18.2 million in 1994, or $1.10 and $0.93 per share, respectively.

LIQUIDITY AND CAPITAL RESOURCES

Since its inception, the Company has financed its operations primarily through the sale of equity securities, raising net proceeds aggregating approximately $180 million as of December 31, 1996 from the private and public sale of such securities. The Company has also financed a portion of its operations through contract research and development revenue, portions of which were paid in advance of work being performed, offsetting the Company's cash usage for operations.

As of December 31, 1996, the Company had cash, cash equivalents and short-term investments totaling $77.6 million and working capital of $56.3 million. In comparison, the Company had cash, cash equivalents and short-term investments of $77.4 million and working capital of $60.0 million as of December 31, 1995. The increase resulted from net proceeds of approximately $9 million from the sale of common stock in 1996 and proceeds of $16.2 million from borrowings under a line of credit made available to the Company by Boehringer Ingelheim, offset by the amounts required to fund operating losses, investments in capital equipment, building improvements, and other investments, and to make principal payments on debt and capital lease obligations.

The 1995 agreement with Boehringer Ingelheim provided the Company with a $40 million line of credit, available under certain circumstances and to be used in support of the combined cell adhesion programs. As of December 31, 1996, the outstanding balance under this line of credit was $16.2 million. See Note 3, Long-term debt and commitments. In December 1996, Boehringer Ingelheim made a $10 million milestone payment by purchasing 409,000 shares of Isis common stock. Of the $10 million payment, $6 million has been accounted for as equity and $4 million has been recorded as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. The Company's valuation of the equity portion was based on a number of factors, including restrictions on transferability of the shares sold in the unregistered transaction and other conditions imposed on Boehringer Ingelheim in connection with its ownership of the shares as well as the average closing price of the common stock for the 20 trading days prior to the milestone date.

The Company had long-term debt and capital lease obligations at December 31, 1996 totaling $26.1 million versus $9.7 million at December 31, 1995. This increase primarily resulted from the $16.2

million advance from the Boehringer Ingelheim line of credit, partially offset by principal repayments on existing obligations. The Company expects that its capital lease obligations will increase over time to fund capital equipment acquisitions required for its expanding business. Lease lines will continue to be used by the Company to the extent that the terms thereof remain commercially attractive.

The Company expects to incur substantial additional research and development costs, including costs related to clinical trials, manufacturing costs, and marketing and distribution expenses, and expects losses to continue to increase as the Company's preclinical testing and clinical trial efforts expand. It is the Company's intention to seek additional collaborative research and development relationships with suitable potential corporate partners. There can be no assurance that any agreements resulting from these discussions will successfully reduce the Company's funding requirements, and arrangements with collaborative partners may require the Company to relinquish rights to certain of its technologies, product candidates or products. Additional equity or debt financings will be required, and there can be no assurance that these funds will be available on favorable terms, if at all. If additional funds are raised by issuing equity securities, further dilution to then existing stockholders may result.

Isis anticipates that its existing available cash, cash equivalents and short-term investments, combined with anticipated interest income and contract revenues, will be adequate to satisfy its capital requirements for approximately two years. The Company's future capital requirements will depend on many factors, including continued scientific progress in its research, drug discovery and development programs; the magnitude of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments; changes in the existing collaborative research and development relationships and the ability of the Company to establish additional research and development arrangements; and the cost of manufacturing scale-up and effective commercialization activities and arrangements. If adequate funds are not available, the Company may be required to significantly curtail one or more of its research, drug discovery or development programs.

Uncertainties associated with the length and expense of preclinical and clinical testing of any of the Company's products could greatly increase the cost of development of such product and affect the timing of anticipated revenues from product sales, and failure by the Company to obtain regulatory approval for any product will preclude its commercialization. In addition, the failure by the Company to obtain patent protection for its products may make certain of its products commercially unattractive.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The financial statements and supplementary data of the Company 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 the Company's definitive Proxy Statement which will be filed on or before April 21, 1997 with the Securities and Exchange Commission in connection with the solicitation of proxies for the Company's 1997 Annual Meeting of stockholders to be held on June 6, 1997 (the "Proxy Statement").

The required information concerning Executive Officers of the Company 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 37 of this Report.

(A)(2) INDEX TO FINANCIAL STATEMENT SCHEDULES

None required.

(A)(3) INDEX TO EXHIBITS

See Index to Exhibits on pages 35 through 36.

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"). (1)
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	--	Registrant's Employee Stock Purchase Plan. (3)
10.10	--	Stock Option Agreement with Daniel L. Kisner, dated as of November 29, 1990. (4)

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(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 the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto 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, 1996.

(C) EXHIBITS

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

(D) FINANCIAL STATEMENT SCHEDULES

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

SIGNATURES

Pursuant to the requirements of Section 14 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 14th day of March, 1997.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE, M.D., Ph.D.
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board 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, Daniel L. Kisner, 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 connections therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

SIGNATURES	TITLE	DATE
/s/ STANLEY T. CROOKE, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, Chief Executive Officer and Director (Principal executive officer)	March 14, 1997
/s/ B. LYNNE PARSHALL B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	March 14, 1997
/s/ DANIEL L. KISNER, M.D. Daniel L. Kisner, M.D.	President, Chief Operating Officer and Director	March 14, 1997
/s/ STEPHEN K. CARTER Stephen K. Carter	Director	March 14, 1997
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 14, 1997
/s/ ALAN C. MENDELSON Alan C. Mendelson	Director	March 14, 1997

SIGNATURES	TITLE	DATE
/s/ WILLIAM R. MILLER - ---------- William R. Miller	Director	March 14, 1997
/s/ MARK B. SKALETSKY - ---------- Mark B. Skaletsky	Director	March 14, 1997
/s/ LARRY SOLL - ---------- Larry Soll	Director	March 14, 1997
/s/ JOSEPH H. WENDER - ---------- Joseph H. Wender	Director	March 14, 1997

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 Pharma 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. (12)
10.3	--	Revised form of Incentive Stock Option Agreement under the Plan. (12)
10.4	--	Revised form of Supplemental Stock Option Agreement under the Plan. (12)
10.5	--	Form of Incentive Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (8)
10.6	--	Form of Supplemental Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (8)
10.7	--	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended. (12)
10.8	--	Registrant's Employee Stock Purchase Plan. (2)
10.9	--	Form of Employee Assignment of Patent Rights. (1)
10.10	--	Stock Option Agreement with Daniel L. Kisner, dated as of November 29, 1990. (1)
10.11	--	Amended and Restated Research, Development and Licensing Agreement by and between Isis Pharmaceuticals, Inc. and Novartis dated February 13, 1996 (with certain confidential information deleted). (11)
10.12	--	License Agreement between the Registrant and the National Technical Information Service (U.S. Department of Commerce), dated September 12, 1990 (with certain confidential information deleted). (1)
10.13	--	License Agreement between the Registrant and the PNA Group dated as of January 29, 1992 (with certain confidential information deleted). (3)
10.14	--	Kyowa Saitama Loan Agreement dated as of April 8, 1992; together with related Trust Deed with Assignment of Rents, Security and Fixture Filing dated as of April 8, 1992; Pledge, Assignment and Security Agreement dated as of April 8, 1992; and Promissory Note dated as of April 20, 1992. (3)
10.15	--	Collaborative Research, Development and License Agreement between the Registrant and The Chemo-Sero-Therapeutic Research Institute dated as of July 11, 1992 (with certain confidential information deleted). (4)
10.16	--	Non-Exclusive Patent License Agreement Between the Registrant and Molecular Biosystems, Inc. dated as of September 14, 1992 (with certain confidential information deleted). (5)
10.17	--	Imperial Bank Note and related Credit Terms and Conditions dated December 31, 1993; together with General Security Agreements dated January 11, 1993 and August 26, 1993.(6)

10.18 -- Imperial Bank Note Secured By Deed of Trust dated May 24, 1994; together with related Deed of Trust and Assignment of Rents dated May 24, 1994; and General Security Agreements dated May 24, 1994. (7)

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
10.19	-- Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (9)
10.20	-- Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(10)
23.1	-- Consent of Ernst & Young LLP.
24.1	-- Power of Attorney. Reference is made to page 33.
27.1	-- Financial Data Schedule.

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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 Quarterly Report on Form 10-Q for the quarter ended June 30, 1992 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1992 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1993 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1994 and incorporated herein by reference.

(8) 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.

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

(10) 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.

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

REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors
Isis Pharmaceuticals, Inc.

We have audited the accompanying balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 1996 and 1995, and the related statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 1996. 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, 1996 and 1995, and the results of its operations and cash flows for each of the three years in the period ended December 31, 1996, in conformity with generally accepted accounting principles.

ERNST & YOUNG LLP

San Diego, California
January 23, 1997

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

	DECEMBER 31,	
	1996	1995
Current assets:		
Cash and cash equivalents	$ 37,082	$46,463
Short-term investments	40,542	30,944
Prepaid expenses and other current assets	1,732	1,638
Total current assets	79,356	79,045
Property, plant and equipment, net	15,334	14,631
Patent costs, net	6,157	4,773
Deposits and other assets	458	1,120
	$101,305	$99,569

LIABILITIES AND STOCKHOLDERS' EQUITY

Current liabilities:		
Accounts payable	$ 2,362	$ 997
Accrued payroll and related expenses	1,489	1,249
Accrued liabilities	2,763	2,838
Deferred contract revenues	10,204	8,913
Current portion of long-term debt and capital lease obligations	6,238	5,008
Total current liabilities	23,056	19,005
Long-term debt and capital lease obligations, less current portion	19,864	4,714
Commitments (See Note 3)		
Stockholders' equity:		
Common stock, $.001 par value; 50,000,000 shares authorized, 26,201,000 shares and 25,249,000 shares issued and outstanding at December 31, 1996 and 1995, respectively	26	25
Additional paid-in capital	181,248	172,253
Unrealized gain on investments	178	118
Accumulated deficit	(123,067)	(96,546)
Total stockholders' equity	58,385	75,850
	$101,305	$ 99,569

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

	YEAR ENDED DECEMBER 31,		
	1996	1995	1994
Revenues:			
Research and development revenues under collaborative agreements	$ 22,572	$ 12,966	$ 10,088
Gain on sale of investment	--	--	3,174
Interest income	4,012	3,001	2,251
	26,584	15,967	15,513
Expenses:			
Research and development	45,653	33,175	26,468
General and administrative	6,246	5,402	5,981
Interest expense	1,206	1,102	1,245
	53,105	39,679	33,694
Net loss	$(26,521)	$(23,712)	$(18,181)
Net loss per share	$ (1.04)	$ (1.10)	$ (0.93)
Shares used in computing net loss per share	25,585	21,514	19,542

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY
(IN THOUSANDS)

DESCRIPTION	COMMON STOCK SHARES	COMMON STOCK AMOUNT	ADDITIONAL PAID IN CAPITAL	UNREALIZED GAINS AND (LOSSES)	TOTAL ACCUMULATED DEFICIT	STOCKHOLDERS' EQUITY
Balance at December 31, 1993	18,773	$19	$113,093	$ --	$ (54,653)	$ 58,459
Options exercised and employee stock purchase plan	93	--	418	--	--	418
Issuances of common stock net of repurchases and offering costs	850	1	5,257	--	--	5,258
Compensation relating to the granting of options and stock bonus	--	--	65	--	--	65
Adjustment to beginning balance for change in accounting method, net of income taxes	--	--	--	3,821	--	3,821
Change in unrealized gains and (losses), net of income taxes	--	--	--	(647)	--	(647)
Realized gains on sale of investment	--	--	--	(3,174)	--	(3,174)
Net loss	--	--	--	--	(18,181)	(18,181)
Balance at December 31, 1994	19,716	20	118,833	--	(72,834)	46,019
Options exercised and employee stock purchase plan	318	--	1,702	--	--	1,702
Issuances of common stock net of repurchases and offering costs	5,215	5	51,655	--	--	51,660
Compensation relating to the granting of options and stock bonus	--	--	63	--	--	63
Change in unrealized gains, net of income taxes	--	--	--	118	--	118
Net loss	--	--	--	--	(23,712)	(23,712)
Balance at December 31, 1995	25,249	25	172,253	118	(96,546)	75,850
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 and stock bonus	--	--	9	--	--	9
Change in unrealized gains, net of income taxes	--	--	--	60	--	60
Net loss	--	--	--	--	(26,521)	(26,521)
Balance at December 31, 1996	26,201	$ 26	$181,248	$ 178	$(123,067)	$ 58,385

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	YEAR ENDED DECEMBER 31,		
	1996	1995	1994
Operating activities:			
Net loss	$ (26,521)	$ (23,712)	$ (18,181)
Adjustments to reconcile net loss to net cash provided from (used in) operating activities:			
Depreciation and amortization	2,633	2,814	3,854
Gain on sale of investment	--	--	(3,174)
Issuance of securities in exchange for technology	--	733	--
Compensation related to grant of options and stock bonus	9	63	65
Changes in assets and liabilities:			
Prepaid expenses and other current assets	(94)	(70)	(18)
Accounts payable	1,365	(533)	160
Accrued payroll and related expenses	240	309	106
Accrued liabilities	(75)	784	(662)
Deferred contract revenues	1,291	4,532	2,689
Net cash used in operating activities	(21,152)	(15,080)	(15,161)
Investing activities:			
Short-term investments	(9,598)	(430)	(10,214)
Unrealized gain on investment	60	118	--
Proceeds from the sale of investment	--	--	4,174
Property, plant and equipment	(862)	(1,073)	(870)
Patent costs	(1,439)	(742)	(1,467)
Deposits and other assets	568	629	(865)
Net cash used in investing activities	(11,271)	(1,498)	(9,242)
Financing activities:			
Net proceeds from issuance of equity	8,987	52,629	5,676
Proceeds from long-term borrowing	16,200	--	3,030
Principal payments on debt and capital lease obligations	(2,145)	(2,514)	(5,111)
Net cash provided from financing activities	23,042	50,115	3,595
Net increase (decrease) in cash and cash equivalents	(9,381)	33,537	(20,808)
Cash and cash equivalents at beginning of year	46,463	12,926	33,734
Cash and cash equivalents at end of year	$ 37,082	$ 46,463	$ 12,926
Supplemental disclosures of cash flow information:			
Interest paid	$ 1,150	$ 1,094	$ 1,257
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt and capital lease obligations for acquisitions of property, plant and equipment	$ 2,325	$ 517	$ 58

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1996

1. ORGANIZATION AND SIGNIFICANT ACCOUNTING POLICIES

ORGANIZATION AND BUSINESS ACTIVITY--Isis Pharmaceuticals (the "Company"), was incorporated in California on January 10, 1989. In conjunction with its initial public offering the Company was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc., in April 1991. The Company was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

NET LOSS PER SHARE--Net loss per share is computed using the weighted average number of shares of common stock outstanding during the period.

RESEARCH AND DEVELOPMENT REVENUES AND EXPENSES--Research and development revenues are recorded as earned based on the performance requirements of the collaborative research and development contracts. Payments received in excess of amounts earned are deferred. Research and development costs are expensed as incurred. For the years ended December 31, 1996, 1995 and 1994 costs and expenses of approximately $29,000,000, $18,100,000, and $12,500,000 respectively, were related to collaborative research and development arrangements.

CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS--Cash equivalents and short-term investments consist of highly liquid debt instruments. The Company considers instruments with original maturities of less than 90 days to be cash equivalents. The Company has recorded its cash equivalents and short-term investments at fair market value as of December 31, 1996, and has classified all of its investments as available- for-sale. This category includes all securities which the Company 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 as 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):

	1996	1995
Land	$ 1,163	$ 1,163
Buildings and improvements	12,974	12,918
Equipment	16,311	13,257
Furniture and fixtures	441	364
	30,889	27,702
Less accumulated depreciation	(15,555)	(13,071)
	$ 15,334	$ 14,631

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

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS - (CONTINUED)
DECEMBER 31, 1996

PATENT COSTS--The Company capitalizes certain costs related to patent applications. Accumulated costs are amortized over the estimated economic lives of the patents using the straight-line method, commencing at the time the patents are issued. Accumulated amortization was $112,000 at December 31, 1996 and $57,000 at December 31, 1995.

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.

2. INVESTMENTS

The Company invests its excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. The Company 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. The Company has not experienced any losses on its short-term investments. As of December 31, 1996, 77% of the debt securities held by the Company had a contractual maturity of one year or less, and the remaining 23% of the portfolio was due within 2.5 years.

In May 1993, the Financial Accounting Standards Board issued Statement of Financial Accounting Standards No. 115, "Accounting for Certain Investments in Debt and Equity Securities." The Company adopted the provisions of the new standard for investments held as of or acquired after January 1, 1994. In accordance with the Statement, prior period financial statements have not been restated to reflect the change in accounting principle. The cumulative effect as of January 1, 1994 of adopting the Statement increased the opening balance of stockholders' equity by $3,821,000 to reflect the net unrealized holding gains on securities classified as available-for-sale which were previously carried at lower of cost or market. This unrealized holding gain arose from the Company's investment in equity securities of Vical Incorporated (see Note 6). During the year ended December 31, 1994 the Company sold its entire investment in the equity securities of Vical Incorporated, realizing a net gain of $3,174,000.

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

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS	ESTIMATED FAIR VALUE
DECEMBER 31, 1996		(In Thousands)	
U.S. Treasury securities and obligations of U.S. Government agencies	$ 36,416	$ 165	$ 36,581
U.S. corporate securities	3,948	13	3,961
Total debt securities	$ 40,364	$ 178	$ 40,542

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS	ESTIMATED FAIR VALUE
DECEMBER 31, 1995	(In Thousands)		
U.S. Treasury securities and obligations of U.S. Government agencies	$ 24,839	$ 13	$ 24,852
U.S. corporate securities	5,987	105	6,092
Total debt securities	$ 30,826	$ 118	$ 30,944

3. LONG-TERM DEBT AND COMMITMENTS

In 1992, the Company refinanced one of its buildings by borrowing $2,500,000. The note bears interest of 8.78% per annum. Principal payments of $30,000 plus related interest are due quarterly, with the remaining principal amount of $1,930,000 due in April 1997. The balance of the note at December 31, 1996 was $1,960,000.

In 1993, the Company borrowed $4,812,000 from a bank to finance the building improvements for a chemistry and manufacturing facility in a building already owned by the Company. The term loan, bearing interest at the prime rate plus 2.5%, was to mature in December 1996. The loan has been extended to February 28, 1997 while terms of a permanent extension are negotiated. The loan requires payments of $50,000 per month plus interest and is secured by certain fixtures and building improvements financed by the bank and a pledged $1,500,000 certificate of deposit. This financing arrangement requires maintenance of certain financial ratios and contains other restrictive covenants, including a restriction on dividends. In addition, if the Company's cash and investment balances fall below $20,000,000, monthly principal payments will increase to $100,000. The balance of the note at December 31, 1996 was $3,062,000.

In 1994, the Company borrowed $2,000,000 from a bank to refinance two of its buildings. The loan bears interest at the prime rate plus 2.5%, will mature in December 1998, and requires payments of $6,667 per month plus interest. The loan is secured by the real estate and a pledged $500,000 certificate of deposit. The balance of the note at December 31, 1996 was $1,813,000.

The Company plans to refinance all of the long-term debt secured by its real estate and building improvements as described in the preceding three paragraphs. The Company has received proposals from financial institutions to provide funding for this purpose and expects that the terms will be finalized in the first quarter of 1997.

In 1996, The Company borrowed $16,200,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim. The funds will be used for the purpose of funding research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year US interbanking rate plus 2.0%, determined at the time each advance is made. Interest payments are due twice each year with principal repayment

due seven years after the advance date. The principal may be repaid in cash or stock, at the Company's option. If the Company 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, 1996 was $16,200,000.

The Company leases equipment and certain maintenance and storage facilities under non-cancelable operating and capital leases with terms through February 2007. Annual future minimum payments under operating and capital leases and future maturities of long-term debt as of December 31, 1996 are as follows (in thousands):

	OPERATING LEASES	CAPITAL LEASES	LONG-TERM DEBT
1997	$ 828	$ 1,388	$ 6,781
1998	809	851	3,279
1999	680	821	1,371
2000	466	504	1,371
2001	440	21	1,371
Thereafter	2,274	--	18,780
Total minimum payments	$5,497	3,585	32,953
Less amount representing interest		(520)	(9,916)
Present value of future minimum payments		3,065	23,037
Less current portion		(1,129)	(5,109)
Total		$ 1,936	$17,928

Rent expense for the years ended December 31, 1996, 1995, and 1994 was $520,000, $303,000 and $180,000, respectively. Cost of equipment under capital leases at December 31, 1996 and 1995 was $12,781,000, and $10,456,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 1996, and 1995 was $9,899,000 and $8,694,000, respectively.

4. STOCKHOLDERS' EQUITY

EQUITY OFFERINGS--In June 1995, in conjunction with the extension of its collaborative agreement with the Company, Novartis made an additional equity investment, purchasing 200,000 shares of common stock at $15 per share.

In July 1995, Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28.5 million in cash plus certain license rights. Of the $28.5 million, $21.3 million has been accounted for as equity and $7.2 million has been accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. The Company's valuation of the equity portion was based on a number of factors, including the restrictions on transferability of the shares sold in the unregistered transaction and other conditions imposed on Boehringer Ingelheim in connection with its ownership of the shares as well as the average closing price of the common stock for the 20 trading days prior to the execution of the definitive agreements. This valuation resulted in recording the equity portion of the transaction at $10.67 per share. On February 28, 1995, the date the negotiation of the principal terms of the collaboration was completed and the parties signed a letter of

intent, the closing price of the common stock was $5.63 per share. The closing price of the common stock on July 18, 1995, the date the definitive agreements were executed, was $12.00 per share.

In October 1995, the Company completed a public offering of 2,875,000 shares of its common stock at $10.00 per share, 700,000 shares of which were acquired by Novartis. The net proceeds of this offering amounted to $27.0 million.

In 1996, Isis achieved a milestone specified under the terms of its collaborative agreement with Boehringer Ingelheim. As a result of this accomplishment, in December 1996, Boehringer Ingelheim purchased 409,000 shares of common stock for $10,000,000 in cash. Of the $10,000,000 payment, $6,000,000 has been accounted for as equity and $4,000,000 has been recorded as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. The Company's valuation of the equity portion was based on the same factors as were used in connection with Boehringer Ingelheim's July 1995 investment. This valuation resulted in recording the equity portion of the transaction at $14.67 per share. The closing price of the common stock on November 18, 1996, the date the parties agreed that the milestone criteria had been achieved, was $16.13 per share.

STOCK OPTION PLANS AND OTHER EMPLOYEE OPTION GRANTS--In June 1989, the Company adopted a stock option plan which provides for the issuance of incentive and non-qualified stock options for the purchase of up to 8,200,000 shares of common stock to its key employees and certain other individuals. In addition to the options issued under the terms of the 1989 plan, options to purchase 319,000 shares of common stock have been granted to certain employees. Typically options expire ten years from the date of grant. Options granted after December 31, 1995 vest over a four year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vest over a five year period. At December 31, 1996, a total of 2,515,000 shares were exercisable, with an aggregate exercise price of $16,851,000. As of that date, 8,200,000 shares had been reserved for issuance under the 1989 plan, of which 1,455,000 were available for future grant. In January 1993, the Board of Directors amended the plan to include provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. The Company has recorded compensation expense of $832,000 for the difference between the grant price and the deemed fair value for financial statement purposes related to options granted between November 1990 and the completion of the Company's initial public offering that have vested.

In July 1992, the Company 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 ten years from the date of grant. Options granted after December 31, 1995 become exercisable in four equal annual installments beginning one year after the date of grant. Options granted before January 1, 1996 vest over a five year period. At December 31, 1996, 73,000 shares issued under this plan were exercisable and 114,000 Shares were available for future grant.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS - (CONTINUED)
DECEMBER 31, 1996

The following table summarizes stock option activity for the years ended December 31, 1996 and 1995 (in thousands, except per share data):

	NUMBER OF SHARES	PRICE PER SHARE
Outstanding at December 31, 1994	4,301	$ .14 to $19.75
Granted	1,698	3.75 to 15.00
Exercised	(253)	.14 to 12.75
Terminated	(300)	3.75 to 16.25
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

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 12/31/96	WEIGHTED AVERAGE REMAINING CONTRACTUAL LIFE	WEIGHTED AVERAGE EXERCISE PRICE	NUMBER EXERCISABLE AS OF 12/31/96	WEIGHTED AVERAGE EXERCISE PRICE
$0.14 - $4.00	1,185	6.34	$3.13	597	$2.33
$4.13 - $6.50	1,185	6.74	$5.73	657	$5.76
$6.63 - $8.25	1,119	6.78	$7.09	699	$7.13
$8.50 - $12.63	1,167	7.26	$10.78	473	$10.20
$12.75 - $14.75	1,053	8.83	$13.25	75	$13.72
$14.81 - $20.00	384	8.51	$17.48	86	$16.15
$0.14 - $20.00	6,093	7.24	$8.48	2,587	$6.73

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 1996, 75,000 shares were issued to employees at prices ranging from $3.40 to $11.16 per share.

STOCK-BASED EMPLOYEE COMPENSATION--The Company 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, the Company's net loss and net loss per share would have been changed to the following pro forma amounts (in thousands, except per share amounts):

	1996	1995
Net loss - as reported	$ (26,521)	$ (23,712)
Net loss - pro forma	(32,200)	(25,100)
Loss per share - as reported	$ (1.04)	$ (1.10)
Loss per share - pro forma	(1.26)	(1.17)

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 both 1995 and 1996: expected life of one year for regular employees, two years for Directors and Vice Presidents, and four years for Executive Officers; expected dividend yield of zero percent and expected volatility of 60 percent. Risk-free interest rate was based on the Treasury Bill rate at the end of each quarter during 1995 and 1996. All options granted during the quarter were valued using the same risk-free rate for the quarter. The weighted average fair value of options granted was $4.01 for 1995 and $7.20 for 1996. The effect of applying FAS 123 pro forma data as provided herein is not necessarily representative of future net operating results.

WARRANTS--The Company has issued warrants in connection with a strategic alliance with PerSeptive Biosystems, Inc. See Note 6.

5. INCOME TAXES

The Company accounts for income taxes pursuant to FASB Statement No. 109, Accounting for Income Taxes.

Significant components of the Company's deferred tax assets as of December 31, 1996 and 1995 are shown below. Valuation allowances of $55,313,000 and $43,200,000 have been recognized for 1996 and 1995, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	1996	1995
Deferred tax assets:		
Capitalized research expense	$ 6,287,000	$ 5,200,000
Net operating loss carryforwards	42,136,000	32,040,000
Research and development credits	5,683,000	5,282,000
Other	3,131,000	2,730,000
Total deferred tax assets	57,237,000	45,252,000
Deferred tax liabilities:		
Patent expense	(1,924,000)	(2,052,000)
Total deferred tax liabilities	(1,924,000)	(2,052,000)
Total net deferred tax assets	55,313,000	43,200,000
Valuation allowance for deferred tax assets	(55,313,000)	(43,200,000)
Net deferred tax assets	$ 0	$ 0

At December 31, 1996, approximately $1,391,000 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, 1996, the Company had federal and California tax net operating loss carryforwards of approximately $119,076,000, and $7,654,000, respectively. The Company also had federal and California research credit carryforwards of approximately $4,506,000 and $1,812,000, 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. The California tax loss carryforward began expiring in 1996.

Annual use of the Company's 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, the Company believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. RESEARCH AND DEVELOPMENT COLLABORATIVE ARRANGEMENTS

In September 1990, the Company entered into a five-year collaborative agreement with Ciba-Geigy Limited ("Ciba") to discover and investigate oligonucleotide compounds active against four specific targets. Both Ciba and the Company have certain licensing and royalty rights under conditions set forth in the agreement. In February 1995, this agreement was extended for an additional three years. Under the agreement, the Company will receive maximum yearly amounts based on the level of scientific resources expended on the program. The program may be terminated based on certain limited circumstances.

In May 1995, Ciba accepted ISIS 5132/CGP 69846A, a novel antisense compound arising from the research collaboration, as a development compound. In September 1995, Isis and Ciba signed a letter of intent to broaden the companies antisense research and development collaboration to include the development of ISIS 3521/CGP 64128A, an anticancer compound that is an antisense inhibitor of protein kinase C (PKC)-a. The broadened collaboration will also include research to discover additional therapeutic compounds. Under the terms of the expanded collaboration, Ciba will fund the development of both ISIS 3521/CGP 64128A and ISIS 5132/CGP 69846A. Isis will receive certain milestone payments from Ciba as these compounds and subsequent compounds arising out of the expanded research program progress through development. Ciba will market these compounds worldwide and will pay Isis a royalty based on sales. In February 1996, Isis and Ciba signed a definitive agreement incorporating the terms of the broadened collaboration. In 1996, Ciba agreed to merge with Sandoz forming a new company known as Novartis. Included in the statement of operations for the years ended December 31, 1996, 1995 and 1994 are contract revenues arising from this collaboration totaling $14,003,000, $7,308,000 and $5,018,000, respectively.

As part of the expanded collaborative relationship, Ciba also made additional equity investments in Isis totaling $10,000,000 in 1995. In June 1995, Ciba made a private equity investment purchasing 200,000 shares for $3,000,000. In October 1995, Ciba purchased an additional 700,000 shares for $7,000,000 as part of the Company's public offering. As of December 31, 1996, Ciba owned approximately 9% of the outstanding common stock of the Company.

In December 1990, the Company entered into an agreement for a collaborative research program with Eisai Co., Ltd. ("Eisai") to discover and investigate oligonucleotide compounds active against CMV, which terminated in March 1994 with the identification of and initiation of clinical development of a compound arising out of this research program. Both Eisai and the Company have certain licensing and royalty rights under conditions set forth in the agreement. Included in the statement of operations is contract revenue of $298,000 for the year ended December 31, 1994. As a result of the collaboration efforts under this program, in December 1992, the Company entered into a co-development agreement with Eisai to develop a specific oligonucleotide compound for North American and European markets. Under the agreement, the Company was responsible for funding 50% of the development activities on a quarterly basis. In August 1996, Isis reacquired full ownership of the development compound in exchange for a royalty on future sales. The Company will be responsible for funding all future development costs of this compound. Included in the statement of operations are co-development revenues of $3,788,000, $2,720,000, and $1,698,000 for the years ended December 31, 1996, 1995 and 1994, respectively.

In 1992, the Company entered into an exclusive license and development agreement with Vical related to certain lipid formulations technology. In connection with the agreement, the Company paid an initial licensing fee of $500,000 and has made payments of $250,000 related to deliverables which were included in the statement of operations as research and development expenses for the year ended December 31, 1992. To maintain its license, the Company paid an additional $250,000 in 1993 related to Vical deliverables. Under the agreement, the Company is required to make additional payments in connection with reaching development-related milestones for Company products incorporating this technology, and is required to pay royalties on certain future sales of such products, if any. In connection with this agreement, the Company purchased equity securities of Vical, which were sold during 1994, resulting in a net gain of $3,174,000.

In July 1992, the Company entered into a three-year collaborative research, development and license agreement with the Chemo-Sero-Therapeutic Research Institute ("Kaketsuken") to discover and develop antisense compounds active against Hepatitis C. Kaketsuken was collaborating in this program with Mochida Pharmaceutical Co., Ltd. ("Mochida"). In July 1995, Mochida terminated its participation in the collaboration. The Company received contract revenues related to this agreement of $450,000 and $952,000 for the years ended December 31, 1995 and 1994, respectively. Kaketsuken will have certain rights to develop and market compounds arising out of the collaboration in Japan for the payment of royalties. The parties have certain other rights and obligations as set forth in the agreement.

In March 1993, the Company entered into a strategic alliance with PerSeptive Biosystems, Inc. ("PerSeptive") for pursuing the development of tools for synthesis, purification and analysis of oligonucleotides. Under the agreements, the Company and PerSeptive receive payments for research and development services and PerSeptive will have the option to commercialize novel purification, analysis, and synthesis products developed as part of the alliance. In conjunction with financing this alliance, a special purpose corporation, PerIsis I, was created. The Company issued, to investors in PerIsis I, six-year Class A warrants to purchase 449,123 shares of its common stock at an exercise price of $8.75 per share. In addition, the Company issued to investors in PerIsis I Class B warrants to purchase a number of shares equal to $800,000 divided by an amount approximating the price per share at the date that the Company's buyout option for PerIsis I stock lapses pursuant to the agreement. In September 1995, the Company purchased all of the outstanding shares of PerIsis I for $1,000 and exchanged 140,000

shares of restricted common stock for all of the outstanding Class B warrants. The Company also agreed to reduce the strike price of Class A warrants to $7.75 per share. The Company recorded a charge of $733,000 to research and development expense in 1995 related to this repurchase of rights in PerIsis I. As of December 31, 1996, all of the Class A warrants remain outstanding.

The Company entered into a research contract with PerIsis I, agreeing to share its knowledge and perform further research into the synthesis, purification and analysis of oligonucleotides. Under this agreement the Company has received approximately $2,400,000 of which approximately $315,000 represents value attributed to the Company's warrants issued as part of the transaction. During the year ended December 31, 1994, the Company recorded revenues related to this research agreement totaling $1,089,000. Recorded revenue was net of warrant amortization of $160,000 in 1994 .

In July 1995, the Company and Boehringer Ingelheim International GmbH ("Boehringer Ingelheim") signed the definitive agreements and completed the formation of a major collaboration in cell adhesion drug design, discovery, development and commercialization. Consistent with the terms of the agreement outlined in the letter of intent, which was signed in February 1995, 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 has been accounted for as equity and $7,200,000 has been accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. In December 1996, Boehringer Ingelheim made a $10,000,000 milestone payment by purchasing 409,000 shares for $10,000,000. Of that total, $6,000,000 has been accounted for as equity and $4,000,000 as deferred revenue. The agreement also provides that Boehringer Ingelheim is entitled to designate one member for election to Isis' Board of Directors. As of December 31, 1996 Boehringer Ingelheim owns approximately 9% of the outstanding common stock of the Company. Boehringer Ingelheim and the Company 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, 1996, the outstanding balance under this line of credit was $16,200,000. The statement of operations for the years ended December 31, 1996 and 1995 reflect contract revenues of $4,024,000 and $1,267,000, respectively, from this collaboration.

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-3 No. 33-72124, 33-75068 and 33-96138 and Form S-8 No. 33- 51236, 33-42970, 33-42356, 33-54840, 33-58450, 33-43330, 33-75150, 33-90780 and 333-05825) of Isis Pharmaceuticals, Inc. of our report dated January 23, 1997, with respect to the financial statements of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 1996.

ERNST & YOUNG LLP

San Diego, California
March 24, 1997

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THIS SCHEDULE CONTAINS SUMMARY FINANCIAL INFORMATION EXTRACTED FROM THE COMPANY'S AUDITED BALANCE SHEET AS OF DECEMBER 31, 1996 AND AUDITED STATEMENTS OF OPERATIONS FOR THE TWELVE MONTHS ENDED DECEMBER 31, 1996 AND IS QUALIFIED IN ITS ENTIRET BY REFERENCE TO SUCH FINANCIAL STATEMENTS.

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