AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON FEBRUARY 17, 1999

REGISTRATION NO. 333-71911

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 1
TO

FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

ISIS PHARMACEUTICALS, INC.
(Exact name of Registrant as specified in its charter)

Delaware	33-0336973
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

2292 Faraday Avenue
Carlsbad, California 92008
(760) 931-9200
(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

B. Lynne Parshall, Esq.
Executive Vice President
ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, California 92008
(760) 931-9200
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:
D. Bradley Peck, Esq.
Scott R. Cutler, Esq.
COOLEY GODWARD LLP
4365 Executive Drive
San Diego, CA 92121
(619) 550-6000

Approximate date of commencement of proposed sale to the public: As soon as practicable after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. [ ]

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. [ ]

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. [ ]

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. [ ]

If delivery of the prospectus is expected to be made pursuant to rule 434, please check the following box. [ ]

THE REGISTRANT HEREBY AMENDS THIS REGISTRATION STATEMENT ON SUCH DATE OR DATES AS MAY BE NECESSARY TO DELAY ITS EFFECTIVE DATE UNTIL THE REGISTRANT SHALL FILE A FURTHER AMENDMENT THAT SPECIFICALLY STATES THAT THIS REGISTRATION STATEMENT SHALL THEREAFTER BECOME EFFECTIVE IN ACCORDANCE WITH SECTION 8(a) OF THE SECURITIES ACT OF 1933 OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(a), MAY DETERMINE.

Subject to Completion, dated February 17, 1999

PROSPECTUS

4,000,000 SHARES

ISIS PHARMACEUTICALS, INC.

COMMON STOCK

All of the shares of Common Stock offered hereby are being sold by Isis. The price of such shares will be determined by negotiations between Isis and the purchasers. Isis' Common Stock is traded on the Nasdaq National Market under the symbol "ISIP". On February 4, 1999, the last reported sale price for the Common Stock on the Nasdaq National Market was $12.75 per share.

INVESTING IN THE COMMON STOCK INVOLVES CERTAIN RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 4.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THE SECURITIES OR PASSED UPON THE ACCURACY OR ADEQUACY OF THIS PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

	Price to the Public	Discounts, Fees and Commissions	Proceeds to the Company (1
Per Share	$	0	$
Total	$	0	$

(1) Before deducting expenses of the offering payable by the Company, estimated at $100,000.

The date of this Prospectus is , 1999

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

NO PERSON IS AUTHORIZED IN CONNECTION WITH ANY OFFERING MADE HEREBY TO GIVE ANY INFORMATION OR TO MAKE ANY REPRESENTATION NOT CONTAINED OR INCORPORATED BY REFERENCE IN THIS PROSPECTUS, AND ANY INFORMATION OR REPRESENTATION NOT CONTAINED OR INCORPORATED HEREIN MUST NOT BE RELIED UPON AS HAVING BEEN AUTHORIZED BY THE COMPANY. THIS PROSPECTUS DOES NOT CONSTITUTE AN OFFER TO SELL, OR A SOLICITATION OF AN OFFER TO BUY, BY ANY PERSON IN ANY JURISDICTION IN WHICH IT IS UNLAWFUL FOR SUCH PERSON TO MAKE SUCH OFFER OR SOLICITATION. NEITHER THE DELIVERY OF THIS PROSPECTUS AT ANY TIME NOR ANY SALE MADE HEREUNDER SHALL, UNDER ANY CIRCUMSTANCES, IMPLY THAT THE INFORMATION HEREIN IS CORRECT AS OF ANY DATE SUBSEQUENT TO THE DATE HEREOF.

AVAILABLE INFORMATION

The Company is subject to the informational requirements of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and in accordance therewith files reports, proxy statements and other information with the Securities and Exchange Commission (the "Commission"). Such reports, proxy statements and other information filed by the Company may be inspected and copies at the public reference facilities maintained by the Commission at 450 Fifth Street, N.W., Washington, D.C. 20549, and at the Commission's following regional offices: Chicago Regional Office, 500 West Madison Street, Chicago, Illinois 60661; and New York Regional Office, Seven World Trade Center, Suite 1300, New York, New York 10048. Copies of such material can also be obtained at prescribed rates from the Public Reference Section of the Commission at 450 Fifth Street, N.W., Judiciary Plaza, Washington, D.C. 20549. The Commission also maintains a site on the World Wide Web that contains reports, proxy and information statements and other information regarding the Company. The address for such site is http://www.sec.gov.

The Company has filed with the Commission a Registration Statement on Form S-3 under the Securities Act of 1933, as amended (the "Securities Act"), with respect to the Common Stock offered hereby. This Prospectus does not contain all of the information set forth in the Registration Statement, certain parts of which are omitted in accordance with the rules and regulations of the Commission. For further information with respect to the Company and the Common Stock offered hereby, reference is made to the Registration Statement and the exhibits and schedules thereto, which may be inspected without charge at, and copies thereof may be obtained at prescribed rates from, the Public Reference Section of the Commission at 450 Fifth Street, N.W., Washington, D.C. 20549.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

Isis' Annual Report on Form 10-K for the fiscal year ended December 31, 1997, and Isis' Quarterly Reports on Form 10-Q for the quarters ended March 31, 1998, June 30, 1998 and September 30, 1998, the Company's Proxy Statement for the 1998 Annual Meeting of Stockholders filed pursuant to Rule 14a-6 of the Exchange Act, and the description of the Common Stock contained in the Company's Registration Statement on Form 8-A filed on April 2, 1991, each as filed with the Commission, are hereby incorporated by reference in this Prospectus except as superseded or modified herein.

All documents filed with the Commission pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this Prospectus and prior to the termination of the offering shall be deemed to be incorporated by reference into this Prospectus and to be a part hereof from the date of filing of such documents. Any statement contained in any document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded for purposes of this Prospectus to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement. Any such statement so modified or superseded shall not be deemed, except as modified or superseded, to constitute a part of this Prospectus.

Isis will provide without charge to each person, including any beneficial owner, to whom this Prospectus is delivered, upon written or oral request of such person, a copy of any and all of the documents that have been or may be incorporated by reference herein (other than exhibits to such documents which are not specifically incorporated by reference into such documents). Such requests should be directed to the Vice President of Finance at Isis' principal executive offices at 2292 Faraday Avenue, Carlsbad, California 92008, telephone number (760) 931-9200.

PROSPECTUS SUMMARY

The following summary is qualified in its entirety by reference to the more detailed information and consolidated financial statements appearing elsewhere or incorporated by reference in this Prospectus.

THE COMPANY

Isis was incorporated in California in January 1989 and in April 1991 changed its state of incorporation to Delaware. Our executive offices are located at 2292 Faraday Avenue, Carlsbad, California 92008, and our telephone number is (760) 931-9200. Isis' World Wide Web address is http://www.isip.com. Information contained in our World Wide Web site should not be considered to be part of this Prospectus.

In February 1999, Dr. Daniel Kisner, President, Chief Operating Officer and a director of Isis, resigned all positions to assume the position of Chief Executive Officer of Caliper Technologies, a privately held biotechnology Company. Dr. Debby Jo Blank joined the Company as Executive Vice President overseeing corporate development, business development, strategic planning and marketing, human resources and operations, and investor relations. B. Lynne Parshall, Executive Vice President and Chief Financial Officer assumed responsibility for the Company's manufacturing and regulatory affairs activities in addition to her previous responsibilities.

Isis Pharmaceuticals is a trademark of Isis. Vitravene(TM) is a trademark of CIBA Vision Corporation. All other brand names or trademarks appearing in this Prospectus are the property of their respective holders.

THE OFFERING

Common Stock offered hereby	4,000,000 shares
Common Stock outstanding after the offering	31,147,000 shares(1)
Use of proceeds	For research, drug discovery and development activities, including preclinical and clinical studies, production of compounds for such studies and capital expenditures, and other general corporate purposes. See "Use of Proceeds."
Nasdaq National Market symbol	ISIP

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(1) Based on shares outstanding as of January 31, 1999. Does not include 7,606,730 shares of Common Stock issuable upon exercise of outstanding options or 1,248,001 shares of Common Stock issuable upon exercise of outstanding warrants as of January 31, 1999.

RISK FACTORS

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

UNCERTAINTY ASSOCIATED WITH CLINICAL TRIALS

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration ("FDA") regulations, to show the safety and effectiveness ("efficacy") of each of our drug candidates, as well as its optimum dosage, before the FDA can approve a drug candidate for sale.

To begin the process, preclinical studies are conducted, first in the research laboratory and then in animals, to identify potential safety problems. For certain diseases, there are animal models that we believe will predict the effects of the drug candidate in humans. For these diseases, a drug candidate is first tested in such an animal model. For several of our drug candidates, no such animal model exists, so evidence of the drug candidate's efficacy must wait until testing on humans. If the research and preclinical development support further development, we must then submit an Investigational New Drug ("IND") application to the FDA to obtain authorization for human clinical testing. However, our IND application may not be granted by the FDA.

Clinical trials are typically conducted in three sequential phases, although the phases may overlap. In Phase I, which typically involves giving the drug to healthy human subjects before giving it to patients, the drug candidate is tested for safety and tolerance. Phase II typically involves studies in a somewhat larger population of diseased patients to identify possible negative effects and safety risks, to begin gathering preliminary efficacy data and to investigate possible dose sizes and schedules. Phase III trials further evaluate the drug's efficacy and further test for safety within an expanded patient population. Each trial follows certain standards and procedures set out in a scientific document, called a protocol, that describes the objectives of the study, the standards to be used to monitor safety and the efficacy criteria to be measured. Each proposed study protocol must be submitted to the FDA as part of the IND. In addition, in the United States, each clinical study is observed by an independent Institutional Review Board ("IRB"). The IRB will consider, among other things, ethical factors, the safety of human subjects and patients and the possible liability of the study center. Foreign countries have similar protocol review procedures and review boards.

Even when human clinical trials are authorized, such testing of any of our current or future drug candidates may not be completed within the specified time period, if at all. The rate of patient enrollment is a critical factor in determining whether a clinical trial will be completed. Patient enrollment depends upon many different factors, including the number of patients suffering from the disease, the type of procedure involved in the trial, whether patients live near the clinical site and if patients meet the criteria to allow them to participate in the study. Delays in planned patient enrollment may result in significant increased costs and delays to us.

We, the FDA or foreign regulatory agencies may also suspend clinical trials at any time if it is shown that the subjects or patients participating in such trials are being exposed to unacceptable health risks. Clinical testing may show any current or future drug candidate to be unsafe or ineffective, and the FDA or foreign regulatory agency might not approve any such product.

Once the clinical trials are completed, data from preclinical testing and clinical trials are submitted to the FDA in a New Drug Application ("NDA") in order to obtain approval to sell the drug. Preparing an NDA involves considerable data collection, verification, analysis and expense. The NDA often takes months to prepare. NDA approval may not be granted on a timely basis, if at all. A number of factors are weighed by the FDA in the approval process, including the severity of the disease, whether other treatments are currently available and the risks and benefits demonstrated in clinical trials. The FDA may deny an NDA if applicable regulatory criteria are not satisfied. The FDA may also require additional testing or information prior to approval, or approve the application but require post-marketing testing and surveillance to monitor the safety of the drug. Quality control and appropriate manufacturing procedures are also conditions for NDA approval. We must submit a similar separate application to foreign regulatory agencies for their review in order to obtain approval to sell the drug in other countries.

NO ASSURANCE OF REGULATORY APPROVAL

Our ongoing research and development activities, as well as the production and marketing of our products, are regulated by many federal, state and local governmental authorities in the United States. Similar regulatory authorities exist in other countries where we intend to test and market our products. Various federal, state and foreign statutes also affect the labeling, storage and record keeping of drug products. The regulatory process, which includes preclinical and clinical testing of each drug candidate to establish its safety and effectiveness, can take many years and is very expensive. Data obtained from

preclinical and clinical activities can be interpreted in different ways, which could delay, limit or prevent FDA or other regulatory approval. If FDA drug approval policies change during the period of product development and regulatory review, delays or rejections can also result. We, our licensees or our marketing partners may encounter similar delays, difficulties or unanticipated costs in foreign countries. Therefore, even after spending significant amounts of time, money, and effort, regulatory approval may not be obtained for drugs developed by us in the United States or in other countries in which we wish to sell those drugs.

Even if regulatory approval of a drug is granted, the approval may limit the drug to certain uses or "indications." Additional clinical trials may be necessary to obtain approval for the use of a drug for any additional indications. An approved drug, we as its manufacturer and our manufacturing facilities are also subject to continual review and periodic inspections by the FDA or foreign regulatory agencies, even after the drug is on the market. As a manufacturer, we must spend considerable time, money and effort, especially in the areas of production and quality control, to comply with FDA or foreign manufacturing regulations. Later discovery of previously unknown problems with a product or facility may result in restrictions being placed on us or that product, including forcing a withdrawal of the product from the market. If our manufacturing facility is not approved or that approval is withdrawn, it can take a considerable amount of time to obtain recertification or to certify a new facility. Our failure to comply with applicable regulatory requirements could, among other things, result in fines, suspensions of regulatory approvals, product recalls, operating restrictions and criminal prosecution. Additional government regulations may be created in the future that could prevent or delay regulatory approval of our products.

NO ASSURANCE OF MARKET ACCEPTANCE

We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which has achieved limited market acceptance in a small commercial market with significant competition. We cannot guarantee that any of our products in development, if approved for marketing, will achieve market acceptance. The degree of market acceptance depends upon a number of factors, including the receipt and scope of regulatory approvals, the establishment and demonstration in the medical and patient advocacy community of the clinical efficacy and safety of our product candidates and their potential advantages over competitive products, and reimbursement policies of government and third-party payors. In addition, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will accept and utilize any products that may be developed by us.

DEPENDENCE ON COLLABORATIVE PARTNERS

We have relied on certain established pharmaceutical companies interested in our technology and products to pay for a portion of our research and development expenses. We have entered into research, development and distribution agreements with these collaborative partners whereby the partners provide money in exchange for certain research services, product rights or marketing rights related to the products or targets involved. Under certain of these agreements, the collaborative partner has some responsibility for conducting preclinical testing and human clinical trials and for preparing and filing the submission for regulatory approval of the drug candidate with the FDA and foreign regulatory agencies. In addition, certain of these agreements provide for us to receive royalties or other revenues based on sales of products developed or marketed by our corporate partners.

If any collaborative partner fails to successfully develop or sell any product in which we have rights, our business may be negatively affected. While we believe that our collaborative partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in successfully commercialized products. The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program. Collaborative partners may be pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful.

EARLY STAGE OF DEVELOPMENT; TECHNOLOGICAL UNCERTAINTY

We are still at an early stage of development. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development drug candidates based upon antisense technology, a novel technology. Laboratory results obtained in preclinical studies do not necessarily indicate the results that will be obtained in later stages of preclinical development or in human clinical testing. For example, we are attempting to develop products for certain diseases for which no appropriate animal model that might predict efficacy currently exists. As a result, drug candidates for these diseases must advance at least to Phase II human clinical trials before we will have evidence of efficacy outside of the laboratory. Drugs discovered by us may not effectively combat the targeted disease and, even if they work, may not be commercially successful.

CONTINUING OPERATING LOSSES

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

FUTURE CAPITAL NEEDS; UNCERTAINTY OF ADDITIONAL FUNDING

Based on our current operating plan, we believe that our available cash and existing sources of credit, together with the proceeds of this offering and interest earned thereon, will be adequate to satisfy our capital needs until at least the end of 2000. Our future capital requirements will depend on many factors, including continued scientific progress in our research, drug discovery and development programs; the size of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the market acceptance of Vitravene; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments; changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements. Our need for additional funding will also depend upon the cost of manufacturing products on a larger scale and our ability to establish and maintain effective marketing and sales activities and arrangements. If we find that we do not have enough money, additional funds may be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

LIMITED LARGE-SCALE MANUFACTURING EXPERIENCE

Our ability to operate profitably will depend in part on our ability to manufacture our drug products, or to have another company manufacture our products, at a cost low enough to enable us to charge a competitive price to buyers. To successfully establish additional commercial manufacturing capability on a large scale, we must improve our manufacturing processes and reduce our product costs. The manufacture of sufficient quantities of new drugs is typically a time-consuming and complex process. Pharmaceutical products based on chemically modified oligonucleotides have never been manufactured on a large commercial scale. There are a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

POSSIBLE OBSOLESCENCE DUE TO TECHNOLOGICAL CHANGE; COMPETITION

Certain companies, both private and publicly traded, are conducting research and development activities with antisense technology and products. We believe that the investigation of the potential of antisense drugs will continue and may increase as these drug design and development techniques become more widely understood. Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing antisense drugs or other new therapeutic drug candidates that are more effective than any drug candidates that we have been developing. Such competitive development could make our technology and products obsolete or non-competitive before we have had enough time to recover our research, development or commercialization expenses.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will compete with respect to manufacturing

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

DEPENDENCE ON PATENTS AND PROPRIETARY RIGHTS

Our success will depend in part on our ability to obtain patent protection for our products both in the United States and in other countries. We file applications, as appropriate, for patents covering both our products and processes. Patents may not issue from any of these applications. Patent applications in the United States are maintained in secrecy until the patents actually issue, and publication of discoveries in the scientific or patent journals tends to lag behind the date of the actual discoveries by several months. For these reasons, we cannot be certain that we were the first creator of inventions covered by our pending patent applications or that we were the first to file patent applications for such inventions. The claims allowed under any issued patents may not be broad enough to protect our proprietary position in our technology. Even issued patents may be challenged, invalidated or circumvented by third parties, and the rights granted may not provide us with competitive advantage.

We must also avoid both infringing patents issued to our competitors and breaching the technology licenses upon which our products might be based. While we are aware of patent applications and patents belonging to competitors, there is always a possibility that a competitor's patent might require us to alter our products or processes, pay licensing fees or stop certain activities. We may not be able to obtain a license to other required technology or, if obtainable, such technology may not be available at reasonable cost. Such developments would cause financial harm to us.

Costly litigation may also be necessary to enforce any patents issued to us or to determine the scope and validity of others' proprietary rights in court or in administrative proceedings. To determine the priority of inventions, we may find it necessary to participate in interference proceedings declared by the U. S. Patent and Trademark Office or in opposition, nullity or other proceedings before foreign agencies in connection with any of our existing or future patents or patent applications. We may find it necessary to participate, at substantial cost, in International Trade Commission proceedings to reduce or stop importation of goods that would compete unfairly with our products. If required, any of the proceedings described above will result in substantial cost to us.

We also rely on trade secrets and proprietary know-how, which we try to protect, in part, by insisting upon confidentiality agreements with our corporate partners, collaborators, employees and consultants. However, these agreements may be breached, and we may not have adequate remedies for any breach. If this happens, our trade secrets may become known or be independently discovered by competitors.

ABSENCE OF SALES AND MARKETING CAPABILITIES

We have no experience in sales, marketing or distribution. We currently do not sell any products directly. Instead, we sell our Vitravene product through our partner CibaVision which is responsible for all sales and marketing of that product. To market any of our products directly, we must develop an expert marketing and sales force capable of supporting product distribution. We may not be able to build such a sales force at all, or at a reasonable cost, and if we do, our direct sales and marketing efforts may not be successful. As with any new product, our products may not achieve market acceptance in place of existing treatments.

UNCERTAINTIES ASSOCIATED WITH THIRD-PARTY REIMBURSEMENT

Our ability to successfully sell our products 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, HMOs and other organizations. Adequate third-party coverage may not be available to allow 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 our products, the market acceptance of these products will be more difficult.

DEPENDENCE ON KEY EMPLOYEES

We are dependent on the principal members of our management and scientific staff. The loss of these employees might slow the achievement of important development goals. It is also critical to our success to recruit and retain qualified scientific personnel to perform research and development work. Although we believe we will be successful in attracting and keeping skilled and experienced scientific personnel, we may not be able to do so on acceptable terms, because of stiff competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

PRODUCT LIABILITY AND POTENTIAL LIMITS OF INSURANCE COVERAGE

Drugs used in clinical trials and drugs sold on the market may expose us to damages claims resulting from the use of such products. Consumers, sellers or distributors of our products can make these claims. We have obtained limited product liability insurance coverage. However, such coverage is becoming increasingly expensive, and we may not be able to afford to buy enough liability insurance to protect us against all of the product liability losses that could possibly occur.

USE OF HAZARDOUS MATERIALS

Our research and development activities involve the controlled use of hazardous materials, chemicals, viruses and various radioactive compounds. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by local, state and federal regulations, there is still a risk of accidental contamination or injury. If there was such an accident, we could be held liable for any damages that result, which could prove costly. Although we believe that we are in compliance with applicable environmental laws and regulations and currently do not expect to have to spend significant amounts of money for environmental control facilities, we may be required to do so to comply with environmental laws and regulations in the future.

VOLATILITY OF STOCK PRICE

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

ANTI-TAKEOVER PROVISIONS

Our Certificate of Incorporation provides for classified terms for the members of the Board of Directors. Our Certificate also includes a provision (the "Fair Price Provision") that requires at least 66-2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, 15% or more of our voting stockholders, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our Certificate of Incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the Board of Directors, the Chairman of the Board or the President, or by any holder of 10% or more of our outstanding common stock. The classified board, Fair Price Provision and other charter provisions protect us in two ways. First, these provisions may discourage certain types of transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of the stockholders to approve transactions that they think may be in their best interests. Second, the Board of Directors has the authority to fix the rights and preferences of and issue shares of Preferred Stock, which may have the effect of delaying or preventing a change in control of the Company without action by the stockholders.

USE OF PROCEEDS

The net proceeds to be received by the Company from the sale of the 4,000,000 shares of Common Stock being offered hereby are estimated to be $50,900,000 assuming a public offering price of $12.75 per share and after deducting estimated offering expenses.

Companies in the biopharmaceutical industry generally expend significant capital resources in product research and development. The Company anticipates that it will be required to raise substantial additional capital over a period of several years in order to finance its research and development programs. Such capital may be raised through additional public or private financings, as well as collaborative relationships, borrowings and other available sources.

The Company intends to use the net proceeds of this offering for its research, drug discovery and development programs and for other general corporate purposes. Expenses to be funded with the offering proceeds include costs of preclinical and clinical studies, the production of compounds for such studies and capital expenditures. The Company has not identified precisely the amounts it plans to spend on each research, drug discovery and development program or the timing of such expenditures. The Company, however, currently plans that approximately 80% of the proceeds will be used for product development, including clinical trials, preclinical studies, manufacturing scale-up and facilities and equipment acquisition. The remaining proceeds will be used to expand selected research activities and for general and administrative purposes. The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the progress of the Company's research, drug discovery and development programs, the results of preclinical and clinical studies, the timing of regulatory approvals, technological advances, determinations as to commercial potential of the Company's compounds and the status of competitive products. In addition, expenditures will also depend upon the establishment of collaborative research arrangements with other companies, the availability of other financing and other factors.

Other methods of financing its operations, including the acquisition of tenant improvements and capital equipment, such as mortgage or lease financing, may be used by the Company if available on attractive terms. In the past, Isis has made a practice of using lease financing for equipment purchases and intends to continue to do so in the future to the extent the terms of such financing remain commercially attractive. To the extent such financing is used, proceeds of this offering will be reallocated to working capital.

Based upon its current operating plan, the Company believes that its available cash and existing sources of credit, together with the proceeds of this offering and interest earned thereon, will be adequate to satisfy its capital needs until at least the end of 2000.

Proceeds of this offering may also be used to acquire companies or products that complement the business of Isis. No such transactions are being planned or negotiated as of the date of this Prospectus.

DILUTION

The net tangible deficit of the Company at December 31, 1998 was $14,296,000 or approximately $0.53 per share of Common Stock. Net tangible deficit per share represents the amount of the Company's tangible assets less total liabilities, divided by 27,053,000 shares of Common Stock.

Net tangible book value dilution per share represents the difference between the amount per share paid by purchasers of shares of Common Stock in the offering made hereby and the pro forma net tangible book value per share of Common Stock immediately after completion of the offering. After giving effect to the sale of 4,000,000 shares of Common Stock in this offering at an assumed offering price of $12.75 per share and the application of the estimated net proceeds therefrom (after deducting estimated offering expenses) the pro forma net tangible book value of the Company as of December 31, 1998 would have been $36,604,000 or $1.18 per share, an immediate increase in net tangible book value of $1.71 per share to existing stockholders and an immediate dilution in net tangible book value of $11.57 per share to purchasers of Common Stock in the offering, as illustrated in the following table:

Assumed public offering price per share		$12.75
Net tangible book value per share at December 31, 1998	$(.53)	
Increase per share attributable to new investors	$ 1.71	
Pro forma net tangible book value per share after offering		$ 1.18
Net tangible book value dilution per share to new investors		$11.57

To the extent that outstanding options and warrants are exercised, there will be further dilution to new investors.

SELECTED FINANCIAL DATA

The selected financial data set forth below with respect to the Company's statements of operation for the years ended December 31, 1996, 1997, and 1998, and with respect to the balance sheet data at December 31, 1996, 1997, and 1998, are derived from the audited financial statements of Isis Pharmaceuticals, Inc. The data should be read in conjunction with the financial statements, related notes and other financial information incorporated by reference herein.

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

	DECEMBER 31,		
	1998	1997	1996
BALANCE SHEET DATA:			
Cash, cash equivalents and short-term investments	$ 58,848	$ 86,786	$ 77,624
Working capital	40,651	62,573	56,300
Total assets	96,074	117,881	101,305
Long-term obligations, less current portion	77,724	56,452	19,864
Accumulated deficit	(197,116)	(154,133)	(123,067)
Total stockholders' equity (deficit)	(4,186)	34,852	58,385

MANAGEMENT'S DISCUSSION AND ANALYSIS
OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Prospectus, this Prospectus contains forward-looking statements regarding the Company's business and products and their projected prospects and qualities, and the Company's relationships with its corporate partners. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing safe and effective drugs, and the endeavor of building a business around such potential products. Actual results could differ materially from those projected in this Prospectus. As a result, the reader is cautioned not to place undue reliance on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section of this Prospectus entitled "Risk Factors" and are described in additional detail in Isis' Annual Report on Form 10-K for the year-ended December 31, 1997, and in the Company's most recent quarterly report on Form 10-Q, which are on file with the U.S. Securities and Exchange Commission, a copy of which is available from the Company.

Since its inception in January 1989, almost all of the Company's resources have been devoted to its research, drug discovery and drug development programs. The Company is not yet profitable and expects to continue to have operating losses for the next several years. Isis' revenue comes from collaborative research and development agreements with pharmaceutical companies, research grants and interest income. The revenue from the collaboration agreements increases the amount of research and development activity that the Company is able to fund and offsets a portion of its research and development costs. See Item 1, "Business--Collaborative Agreements." In 1998, Isis received approval from the FDA to begin marketing its first product, Vitravene, a drug used to treat CMV retinitis.

RESULTS OF OPERATIONS

Years Ended December 31, 1998 and December 31, 1997

The Company's revenue from collaborative research and development agreements was $38.6 million for the year ended December 31, 1998 compared with $32.7 million in 1997, an increase of 18%. The receipt of $5 million from CpG ImmunoPharmaceuticals, Inc. for a license to certain issued patents together with $1.8 million from a research collaboration with Merck contributed to this revenue increase. Isis delivered its first commercial shipment of Vitravene in 1998, earning product revenue of $0.6 million.

Research and development expenses rose 11% to $62.2 million in 1998 from $55.9 million in 1997. The increase in research and development expenses occurred because compounds in preclinical and clinical development are continuing to advance into more expensive stages of development. We expect that research and development expenses will continue to increase as compounds continue to advance in clinical development.

Operating expenses in 1998 included $5.2 million for acquired in-process research and development. This expense arises from the acquisition of the antisense patent estate from Gilead Sciences, Inc. in December 1998. This acquisition includes patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. No similar expenses were incurred in 1997.

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

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

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

At December 31, 1998, Isis' net operating loss carryforward for federal income tax purposes was approximately $193.5 million. The Company's research credit carryforward for federal income tax purposes was approximately $8.4 million. 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, due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from the Company's net operating loss and tax credit carryforwards. However, there may or may not be additional limitations arising from any future changes in ownership that may have a material adverse impact on the Company.

Isis believes that inflation and changing prices have not had a material effect on the Company's operations to date.

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

Isis' revenue from collaborative research and development agreements was $32.7 in 1997 and $22.7 million in 1996, an increase of 44%. Revenue from collaborative agreements increased because corporate partners paid the Company fees and milestone payments totaling $9 million.

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

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

The Company's net loss was $31.1 million, or $1.17 per share, in 1997 and $26.5 million, or $1.04 per share, in 1996.

LIQUIDITY AND CAPITAL RESOURCES

Isis has financed its operations with revenue from contract research and development, by selling equity securities and by issuing long-term debt. From its inception through December 31, 1998, Isis has earned approximately $145 million in revenue from contract research and development. The Company has also raised net proceeds of approximately $185 million from the sale of equity securities since it was founded. Isis has borrowed approximately $60 million under long-term debt arrangements to finance a portion of its operations.

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

The agreement with Boehringer Ingelheim International GmbH provides the Company with a $40 million line of credit. This line of credit is available under certain circumstances and is to be used to support the collaboration cell adhesion programs. As of December 31, 1998, the outstanding balance under this line of credit was $22.6 million. See Note 3 to the Financial Statements, "Long-term obligations and commitments".

In October 1997, Isis borrowed $25 million in a private transaction. The loan must be repaid on November 1, 2007, and bears interest at 14% per annum. No payments of either principal or interest are required during the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan. No principal payments are required until November 1, 2007. In conjunction with this transaction, Isis issued warrants to purchase 500,000 shares of common stock at a price of $25 per share. On May 1, 1998, the Company completed a follow-on $15 million private debt financing. This financing was a follow-on to the Company's $25 million private debt financing in October 1997 and bears the same terms and conditions. In conjunction with this follow-on transaction, Isis issued warrants to purchase 300,000 shares of common stock at a price of $25 per share. The warrants issued in connection with both of these financings expire on November 1, 2004. The warrants have been valued at combined total of $5.4 million. This amount has been credited to stockholders' equity. Because interest is deferred during the first 5 years, the combined principal balance of both borrowings will accrue to a total of $78 million on November 1, 2002. The debt under these arrangements is carried on the balance sheet net of the unamortized amount allocated to the warrants and including accrued interest. The combined carrying amount of these notes at December 31, 1998 was $41,321,000. See Note 3 to the Financial Statements, "Long-term obligations and commitments".

As of December 31, 1998, the Company's long-term obligations totaled $81.3 million compared to $58.7 million at December 31, 1997. This increase was due to the $15 million follow-on debt financing together with the accrual of interest on the ten-year notes described above. Additional capital lease financing to fund equipment acquisitions also contributed to the increase. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for the Company's growing business. We will continue to use lease lines as long as the terms continue to remain commercially attractive. We believe that the Company's existing cash, cash equivalents and short-term investments, combined with interest income and contract revenue will be sufficient to meet its anticipated requirements for approximately two years.

YEAR 2000 COMPUTER ISSUES

Until recently many computer programs were written to store only two digits of date-related information. Thus the programs were unable to distinguish between the year 1900 and the year 2000. As a result, many computer experts have significant concerns regarding how those programs will function after December 31, 1999. This is frequently referred to as the "Year 2000 Problem." The Company is in the process of reviewing its computer systems and other equipment that utilize embedded microprocessors to assess the potential exposure to this problem. Because Isis was founded in 1989 and all of its computer systems and equipment have been purchased or upgraded since that time, we believe the risk of material disruption to the Company's operations as a result of the presence of this defect in its own computer systems is minimal.

The Company has also requested information from its significant suppliers, corporate partners and financial institutions to ensure that those parties have appropriate plans to address Year 2000 issues where their systems could impact Isis' operations. The Company is assessing the extent to which its operations are vulnerable should those organizations fail to properly modify their computer systems.

A team of Isis employees is conducting the Company's Year 2000 initiative. The team's activities are designed to ensure that there is no adverse effect on the Company's core business operations and that transactions with customers, suppliers, corporate partners and financial institutions are fully supported. The evaluation of these risks is nearing completion. We estimate that any required remediation and validation will be completed by mid-1999. While the Company believes its planning and preparations will be adequate to address its Year 2000 concerns, the Company cannot guarantee that the systems of other companies, on which the Company's systems and operations rely, will be converted on a timely basis and will not have a material effect on the Company. The Company has not yet finalized a formal contingency plan. That plan will be finalized as the risk assessment is completed. The total cost of the Year 2000 risk assessment and remediation is funded through operating cash flows and the Company is expensing these costs as they are incurred. Based on information obtained to date, the cost of identifying and remediating exposures to the Year 2000 Problem is not expected to be material to the Company's results of operations or financial position. The estimated total cost of the Company's Year 2000 assessment and remediation is not expected to exceed $500,000.

PLAN OF DISTRIBUTION

The Common Stock is being offered to a limited number of investors directly by the Company. The price of the Common Stock offered hereby will be determined through negotiations between the Company and the purchasers.

The Company will pay all of the expenses incident to the offering and sale of the Common Stock to the public. Such expenses are estimated to be $100,000.

LEGAL MATTERS

The validity of the issuance of the Common Stock offered hereby will be passed upon for the Company by Grantland E. Bryce, Vice President and General Counsel of the Company. Mr. Bryce does not beneficially own any shares of Common Stock as of the date of this Prospectus.

EXPERTS

The financial statements of Isis Pharmaceuticals, Inc., appearing in Isis Pharmaceuticals, Inc.'s Annual Report on Form 10-K for the year ended December 31, 1997, have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon included therein and incorporated herein by reference. Such financial statements are incorporated herein in reliance upon the reports of Ernst & Young LLP given upon the authority of such firm as experts in accounting and auditing.

INDEX TO FINANCIAL STATEMENTS

REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors
Isis Pharmaceuticals, Inc.

We have audited the accompanying balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 1998 and 1997, and the related statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 1998. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with generally accepted auditing standards. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Isis Pharmaceuticals, Inc. at December 31, 1998 and 1997, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 1998, in conformity with generally accepted accounting principles.

ERNST & YOUNG LLP

San Diego, California
January 30, 1999

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

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

LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

DESCRIPTION	COMMON STOCK SHARES	COMMON STOCK AMOUNT	ADDITIONAL PAID IN CAPITAL	ACCUMULATED OTHER COMPREHENSIVE INCOME	ACCUMULATED DEFICIT	TOTAL STOCKHOLDERS' EQUITY
Balance at December 31, 1995	25,249	$25	$172,253	$ 118	$ (96,546)	$ 75,850
Comprehensive Income						
Net loss	--	--	--	--	(26,521)	(26,521)
Changes in unrealized gains and (losses), net of income taxes	--	--	--	60	--	60
Comprehensive Income	--	--	--	--	--	(26,461)
Options exercised and employee stock purchase plan	543	1	3,164	--	--	3,165
Issuances of common stock net of repurchases and offering costs	409	--	5,822	--	--	5,822
Compensation relating to the granting of options	--	--	9	--	--	9
Balance at December 31, 1996	26,201	26	181,248	178	(123,067)	58,385
Comprehensive Income						
Net loss	--	--	--	--	(31,066)	(31,066)
Change in unrealized gains and (losses),net of income taxes	--	--	--	(13)	--	(13)
Comprehensive Income						(31,079)
Options exercised and employee stock purchase plan	454	1	3,306	--	--	3,307
Issuances of warrants to purchase common stock	--	--	3,780	--	--	3,780
Compensation relating to the granting of options	--	--	459	--	--	459
Balance at December 31, 1997	26,655	27	188,793	165	(154,133)	34,852
Comprehensive Income						
Net loss	--	--	--	--	(42,983)	(42,983)
Change in unrealized gains and (losses), net of income taxes	--	--	--	1	--	1
Comprehensive Income						(42,982)
Options exercised and employee stock purchase plan	398	--	2,298	--	--	2,298
Issuances of warrants to purchase common stock	--	--	1,646	--	--	1,646
Balance at December 31, 1998	27,053	$27	$192,737	$ 166	$(197,116)	$ (4,186)

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1998

1. ORGANIZATION AND SIGNIFICANT ACCOUNTING POLICIES

Organization and business activity--Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, 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.

Basic net loss per share--In 1997, the Financial Accounting Standards Board issued Statement No. 128, "Earnings Per Share." Statement No. 128 replaced the calculation of primary and fully diluted earnings per share with basic and diluted earnings per share. Basic earnings per share excludes any dilutive effects of options, warrants and convertible securities. Dilutive earnings per share includes the dilutive effects of options, warrants and convertible securities. Options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect would be antidilutive. All net losses per share have been presented to conform to Statement No. 128 requirements.

Contract revenues and expenses--Contract revenues are recorded as earned based on the performance requirements of the collaborative research and development contracts. Payments received in excess of amounts earned are recorded as deferred contract revenues. Research and development costs are expensed as incurred. For the years ended December 31, 1998, 1997 and 1996, costs and expenses of approximately $35,000,000, $31,000,000, and $29,000,000 respectively, were related to collaborative research and development arrangements.

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, 1998, 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 in Accumulated Other Comprehensive Income, a separate component of stockholders' equity. See Note 2 - Investments.

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

	DECEMBER 31,	
	1998	1997
Land	$ 1,163	$ 1,163
Buildings and improvements	16,084	13,607
Equipment	25,324	21,599
Furniture and fixtures	1,227	927
	43,798	37,296
Less accumulated depreciation	(22,256)	(18,511)
	$ 21,542	$ 18,785

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

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

Patent costs--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, beginning with the date the patents are issued. Accumulated amortization was $493,000 at December 31, 1998 and $240,000 at December 31, 1997.

Use of estimates--The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

Comprehensive income--The Company adopted Statement of Financial Accounting Standards (FAS) 130, "Reporting Comprehensive Income", at December 31, 1998. Under FAS 130, the Company is required to display comprehensive income and its components as part of the Company's full set of financial statements. The measurement and presentation of net income did not change. Comprehensive income is comprised of net income and certain changes in equity of the Company that are excluded from net income. Specifically, FAS 130 requires unrealized holding gains and losses on the Company's available-for-sale securities, which were reported separately in stockholders' equity, to be included in accumulated other comprehensive income. Comprehensive income for the years ended December 31, 1998, 1997 and 1996 have been reflected in the Consolidated Statement of Stockholders' Equity.

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

2. INVESTMENTS

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

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

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS	ESTIMATED FAIR VALUE
DECEMBER 31, 1998		(in thousands)	
U.S. Treasury securities and obligations of U.S. Government agencies	$20,700	$ 86	$20,786
U.S. corporate debt securities	10,364	80	10,444
Total debt securities	$31,064	$166	$31,230
DECEMBER 31, 1997			
U.S. Treasury securities and obligations of U.S. Government agencies	$32,980	$105	$33,085
U.S. corporate debt securities	15,539	60	15,599
Total debt securities	$48,519	$165	$48,684

3. LONG-TERM OBLIGATIONS AND COMMITMENTS

The Company obtained $25,060,000 in private debt financing during 1997 and an additional $15,000,000 in 1998. The terms of the financing provide for a 10 year maturity on the debt, interest of 14% per annum and deferred interest payments for the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan, November 1, 2007. No principal repayments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $78 million on November 1, 2002. In conjunction with the debt financing, Isis issued warrants to the lender to purchase shares of common stock, exercisable at $25 per share. The Company issued warrants for 500,000 common shares in 1997 and 300,000 shares in 1998. The warrants were valued at $3,780,000 and $1,646,000 respectively, and were credited to equity. The debt is carried on the balance sheet net of the unamortized amount allocated to the warrants, and including accrued interest. The carrying amount at December 31, 1998 was $41,321,000.

In 1997, the Company obtained 2 new term loans from a bank to refinance existing notes secured by real property and to fund facilities expansion. Both notes are secured by the Company's real property and bear interest at the prime interest rate plus 0.5%. The first note in the amount of $3,707,000 requires monthly principal repayments of $12,433 plus interest with the remaining principal balance due in April 2002. The balance of the note at December 31, 1998 was $3,451,000. The second note in the amount of $6,000,000 requires monthly principal repayments of $50,000 plus related interest with the remaining principal balance due in July 2002. The balance at December 31, 1998 was $5,150,000.

In 1996 and 1997, the Company borrowed a total of $22,576,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim International GmbH. The borrowed funds are being used to fund research and development costs associated with the

collaboration. Borrowings under the line of credit bear interest at the 7 year U.S. interbanking rate plus 2.0%, determined at the time each advance is made. Interest payments are due twice each year with principal repayment due 7 years after the advance date. The principal may be repaid in cash or stock, at 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, 1998 was $22,576,000.

In December 1998, the Company purchased from Gilead Sciences, Inc. ("Gilead"), the holdings of its antisense patent estate. This acquisition includes patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over the next three years. Isis made the initial $2,000,000 payment in December 1998. The Company has recorded the net present value of the future payments as a long-term obligation on the balance sheet. The balance of this obligation at December 31, 1998 was $3,238,000.

The Company leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through February 2007. Annual future minimum payments under operating leases and other long-term obligations as of December 31, 1998 are as follows (in thousands):

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

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

4. STOCKHOLDERS' EQUITY

Stock Option Plans and Other Employee Option Grants--In June 1989, 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 10,200,000 shares of common stock to its employees and certain other individuals. In addition to the options issued under the terms of the 1989 plan, non-qualified options to purchase 319,000 shares of common stock have been granted to certain employees. The plan also includes provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. Typically options expire 10 years from the date of grant. Options granted after December 31, 1995 vest over a 4 year period, with 25% exercisable at the end of 1 year from the date of the grant and the balance vesting ratably thereafter.

Options granted before January 1, 1996 generally vest over a 5 year period. At December 31, 1998, a total of 4,347,000 shares were exercisable, and 1,903,000 were available for future grant.

In July 1992, 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 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in 4 equal annual installments beginning 1 year after the date of grant. Options granted before January 1, 1996 vest over a 5 year period. At December 31, 1998, 139,000 shares issued under this plan were exercisable and 58,000 Shares were available for future grant.

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

	NUMBER OF SHARES	PRICE PER SHARE
Outstanding at December 31, 1996	6,093	$ .14 to $20.00
Granted	1,071	13.19 to 19.88
Exercised	(395)	.14 to 16.00
Terminated	(327)	3.75 to 18.25
Outstanding at December 31, 1997	6,442	.14 to 20.00
Granted	1,168	7.06 to 15.44
Exercised	(320)	.14 to 14.50
Terminated	(304)	3.75 to 20.00
Outstanding at December 31, 1998	6,986	.14 to 19.88

The following table summarizes information concerning currently outstanding and exercisable options (in thousands, except contractual life and exercise price data):

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

Employee Stock Purchase Plan--In 1991, the Board of Directors adopted the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance thereunder. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offer or the end of each six-month purchase period. During 1998, 78,000 shares were issued to employees at prices ranging from $10.47 to $10.73 per share. In 1997, 58,000 shares were issued at prices ranging from $10.73 to $15.30 per share. At December 31, 1998, 141,000 shares were available for purchase under this plan.

Stock-Based Employee Compensation--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 basic net loss per share would have been changed to the following pro forma amounts (in thousands, except per share amounts):

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

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

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

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

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

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS - (CONTINUED)
DECEMBER 31, 1998

5. INCOME TAXES

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

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

At December 31, 1998, approximately $3,627,000 of the valuation allowance for deferred tax assets relates to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 1998, the Company had federal and California tax net operating loss carryforwards of approximately $193,526,000 and $33,507,000, respectively. The Company also had federal and California research credit carryforwards of approximately $8,402,000 and $3,765,000, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% limitation in the utilization of California loss carryforwards. The federal tax loss carryforward and the research credit carryforwards will begin expiring in 2004 unless previously utilized.

Approximately $3,100,000 of the California tax loss carryforward expired during 1998 and the related deferred tax asset and tax loss carryforward amounts have been reduced accordingly. The remaining California tax loss carryforward will begin expiring in 1999, unless utilized.

Annual use of 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 1990, Isis entered into a collaborative agreement with Novartis to discover and investigate oligonucleotide compounds active against 4 specific targets. In 1996, Isis and Novartis signed a definitive agreement broadening the companies' antisense research and development collaboration to include the development of ISIS 3521 and ISIS 5132, anticancer compounds that were discovered through the research collaboration. The broadened collaboration also includes research to discover additional therapeutic compounds. Under the terms of the expanded collaboration, Novartis is funding the development of both ISIS 3521 and ISIS 5132. Isis receives certain milestone payments from Novartis as these compounds and subsequent compounds arising out of the expanded research program progress through development. Novartis will market these compounds worldwide and will pay Isis a royalty based on sales. Included in the statement of operations for the years ended December 31, 1998, 1997 and 1996 are contract revenues arising from this collaboration totaling $15,641,000, $21,106,000 and $14,003,000, respectively. As of December 31, 1998, Novartis owned approximately 8% of the outstanding common stock of the Company.

In July 1997, the Company and CIBA Vision Corporation ("CIBA Vision") entered into an agreement granting CIBA Vision exclusive worldwide distribution rights for Vitravene (fomivirsen). Under the terms of the agreement, Isis will manufacture and sell Vitravene to CIBA Vision at a price that will allow Isis and CIBA Vision to share the commercial value of the product. CIBA Vision will market and sell Vitravene worldwide and will be responsible for regulatory approvals outside of the United States and Europe. Additionally, CIBA Vision received the option to acquire the exclusive license to market and distribute a second generation antisense compound to treat CMV retinitis (ISIS 13312) which is currently in development by Isis. In August 1998, the FDA approved Vitravene for marketing, and in the fourth quarter of the year CIBA Vision began selling Vitravene commercially. Isis delivered its first commercial shipment of Vitravene to CIBA Vision in the fourth quarter of 1998 and recorded $560,000 in net product revenues. For the years ended December 31, 1998 and December 31, 1997, Isis also earned contract revenue of $7,500,000 and $5,000,000, respectively, under the CIBA Vision agreement.

In July 1995, the Company and Boehringer Ingelheim International GmbH ("Boehringer Ingelheim") signed definitive agreements and completed the formation of a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28,500,000 in cash plus certain license rights. Of the $28,500,000, $21,300,000 was accounted for as equity and $7,200,000 was accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. In December 1996, coinciding with the achievement of a milestone, Boehringer Ingelheim purchased 409,000 shares for $10,000,000. Of that total, $6,000,000 was accounted for as equity and $4,000,000 as deferred revenue. The agreement also provides that Boehringer Ingelheim is entitled to designate 1 person for election to Isis' Board of Directors. As of December 31, 1998 Boehringer Ingelheim owned approximately 9% of the outstanding common stock of the Company. Boehringer Ingelheim and Isis are providing equal funding for the combined research and development program and will share equally in the profits from all products of the collaboration. Boehringer Ingelheim has also provided Isis with a $40,000,000 line of credit, available under certain circumstances to be used in support of the combined programs. As of December 31, 1998, the outstanding balance under this line of credit was $22,576,000. The statement of operations for the years ended December 31, 1998, 1997 and 1996 reflects contract revenues of $6,544,000, $5,603,000 and $4,024,000, respectively, from this collaboration.

In December 1998, the Company entered into a collaborative research agreement with Zeneca Pharmaceuticals ("Zeneca") to discover, develop and commercialize novel antisense-based cancer drugs. Under the terms of this collaboration, Isis will create and, with Zeneca, screen antisense-based candidates for certain cancer targets. Isis will receive from Zeneca a technology access fee, annual research funding, milestone payments for any drugs progressing into clinical development and royalties on the sales of any marketed drug arising out of the collaboration. The initial term of the research collaboration is three years. In December 1998, Zeneca paid $2,000,000 in technology access fees which was accounted for as deferred revenue.

Also in December 1998, the Company entered into a research collaboration with Abbott Laboratories, Inc. ("Abbott") to prioritize drug development targets using Isis' Antisense Target Validation Technology. The collaboration will enable Abbott to validate numerous gene targets, identify the function of these genes and prioritize the targets. Isis will receive from Abbott an upfront fee, quarterly research fees, milestone payments and royalties on net sales of any Abbott non-antisense product arising from the collaboration. Isis will receive rights to Abbott genes to develop antisense drugs. The initial term of the research collaboration is two years. In December 1998, Isis received an initial payment of $250,000 which was accounted for as deferred revenue.

7. EARNINGS PER SHARE

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

The following table sets forth the computation of basic and diluted earnings per share (in thousands, except per share data):

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

Options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect would be antidilutive. For additional disclosures regarding outstanding stock options and warrants, see Note 4--Stockholders' equity.

4,000,000 SHARES

ISIS PHARMACEUTICALS, INC.

COMMON STOCK

TABLE OF CONTENTS

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all expenses payable by the Registrant in connection with the sale of the 4,000,000 shares of Common Stock being registered. All the amounts shown are estimates except for the registration fee.

SEC registration fee		$ 14,734
Legal fees and expenses		$ 40,000
Accounting fees and expenses		$ 10,000
Nasdaq fees for newly issued shares.....		$ 17,500
Miscellaneous		$ 17,766
Total	$	$100,000

ITEM 15. INDEMNIFICATION OF OFFICERS AND DIRECTORS

Under Section 145 of the Delaware General Corporation Law, the Registrant has broad powers to indemnify its Directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act of 1933, as amended (the "Securities Act").

The Registrant's Certificate of Incorporation and By-laws include provisions to (i) eliminate the personal liability of its directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted by Section 102(b)(7) of the General Corporation Law of Delaware (the "Delaware Law") and (ii) require the Registrant to indemnify its Directors and officers to the fullest extent permitted by Section 145 of the Delaware Law, including circumstances in which indemnification is otherwise discretionary. Pursuant to Section 145 of the Delaware Law, a corporation generally has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are, or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in, or not opposed to, the best interest of the corporation, and with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful. The Registrant believes that these provisions are necessary to attract and retain qualified persons as Directors and officers. These provisions do not eliminate the Directors' duty of care, and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available under Delaware Law. In addition, each Director will continue to be subject to liability for breach of the Directors' duty of loyalty to the Registrant, for acts or omissions not in good faith or involving intentional misconduct, for knowing violations of law, for acts or omissions that the Director believes to be contrary to the best interests of the Registrant or its stockholders, for any transaction from which the Director derived an improper personal benefit, for acts or omissions involving a reckless disregard for the Directors' duty to the Registrant or its stockholders when the Director was aware or should have been aware of a risk of serious injury to the Registrant or its stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the Director's duty to the Registrant or its stockholders, for improper transactions between the Director and the Registrant and for improper distributions to stockholders and loans to Directors and officers. The provision also does not affect a Director's responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

The Registrant has entered into indemnity agreements with each of its Directors and executive officers that require the Registrant to indemnify such persons against expenses, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a Director or an executive officer of the Registrant or any of its affiliated enterprises, provided such person acted in good faith and in a manner such persons reasonably believed to be in, or not opposed to, the best interests of the Registrant and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth certain procedures that will apply in the event of a claim for indemnification thereunder.

At present, there is no pending litigation or proceeding involving a Director or officer of the Registrant as to which indemnification is being sought, nor is the Registrant aware of any threatened litigation that may result in claims for indemnification by any officer or Director.

The Registrant has an insurance policy covering the officers and directors of the Registrant with respect to certain liabilities, including liabilities arising under the Securities act or otherwise.

ITEM 16. EXHIBITS

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
4.1	Amended and Restated Certificate of Incorporation. (1)
4.2	By-laws. (1)
5.1	Opinion of Grantland E. Bryce.
23.1	Consent of Ernst & Young LLP.
23.2	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.
24.1	Power of Attorney. Reference is made to page II-5.
27.1	Financial Data Schedule.

- ----------
(1) Filed as an exhibit to the Registration Statement on Form S-1 (No. 33-39649) or amendments thereto and incorporated herein by reference.

ITEM 17. UNDERTAKINGS

Insofar as indemnification for liabilities arising under the Securities Act of 1933, may be permitted to directors, officers, and controlling persons of the Registrant pursuant to the provisions described in Item 15 or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission, such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer, or controlling person of the Registrant in the successful defense of any action suit, or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that, for the purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) of Section 15(d) of the Securities Exchange Act of 1934 that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant undertakes that; (1) for purpose of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of the registration

statement in reliance upon Rule 430A and contained in the form of prospectus filed by the Registrant pursuant to Rule 424(b) (1) or (4) or 497(h) under the Securities Act shall be deemed to be part of the registration statement as of the time it was declared effective; and (2) for the purpose of determining any liability under the Securities act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Amendment No. 1 to Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 17th day of February, 1999.

ISIS PHARMACEUTICALS, INC.

By: /s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board and Chief Executive Officer
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as his or her true and lawful attorney-in-fact and agents, with full power of substitution and resubstitution, for the undersigned and in his or her name, place and stead, in any and all capacities, to sign any or all amendments (including post-effective amendments) to the Registration Statement and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange commission, granting unto said attorneys-in-fact and agents, and each of them, full power of authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, each acting alone, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Amendment No. 1 to Registration Statement has been signed below by the following persons in the capacities indicated and on the dates indicated.

SIGNATURES	TITLE	DATE
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board and Chief Executive Officer (Principal executive officer)	February 17, 1999
* B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	February 17, 1999
* Alan C. Mendelson	Director	February 17, 1999
* Christopher F.O. Gabrieli	Director	February 17, 1999
* William R. Miller	Director	February 17, 1999
* Mark B. Skaletsky	Director	February 17, 1999
* Larry Soll, Ph.D.	Director	February 17, 1999
* Joseph H. Wender	Director	February 17, 1999
Burkhard Blank	Director	February , 1999

By: /s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Attorney-In-Fact

EXHIBIT INDEX

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(1) Filed as an exhibit to the Registration Statement on Form S-1 (No. 33-39649) or amendments thereto and incorporated herein by reference.

EXHIBIT 5.1

OPINION OF GRANTLAND E. BRYCE

February 4, 1999

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

Ladies and Gentlemen:

You have requested my opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc. (the "Company") of a Registration Statement on Form S-3 (the "Registration Statement") with the Securities and Exchange Commission (the "Commission") covering the offering of 4,000,000 shares of the Company's Common Stock to be sold by certain stockholders, as described in the Registration Statement (the "Common Stock").

In connection with this opinion, I have examined and relied upon the Registration Statement, the Company's Amended and Restated Certificate of Incorporation and Bylaws and the originals or copies certified to our satisfaction, of such records, documents, certificates, memoranda and other instruments as in our judgment are necessary or appropriate to enable me to render the opinion expressed below.

On the basis of the foregoing, and in reliance thereon, I am of the opinion that the Common Stock, when sold in accordance with the Registration Statement, will be validly issued, fully paid and nonassessable.

I consent to the reference to me under the caption "Legal Matters" in the Prospectus included in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

/s/ Grantland E. Bryce
- ------------------------------
Grantland E. Bryce
Vice President, General Counsel

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Amendment No. 1 to Form S-3 No. 333-71911), and related Prospectus of Isis Pharmaceuticals, Inc for the registration of 4,000,000 shares of its common stock to be filed with the Securities and Exchange Commission on February 17, 1999, and to the incorporation by reference therein of our report dated January 23, 1998, with respect to the financial statements and schedule of Isis Pharmaceuticals, Inc. included in its Annual Report on Form 10-K for the year ended December 31, 1997, filed with the Securities and Exchange Commission. We also consent to the use of our report dated January 30, 1999 with respect to the financial statements of Isis Pharmaceuticals, Inc. for the year ended December 31, 1998 in the above mentioned registration statement and prospectus.

ERNST & YOUNG LLP

San Diego, California
February 12, 1999

5

THIS SCHEDULE CONTAINS SUMMARY FINANCIAL INFORMATION DERIVED FROM THE COMPANY'S BALANCE SHEET AS OF DECEMBER 31, 1998 AND STATEMENTS OF OPERATIONS FOR THE YEAR ENDED DECEMBER 31, 1998 AND IS QUALIFIED IN ITS ENTIRETY BY REFERENCE TO SUCH FINANCIAL STATEMENTS.

1,000

YEAR
DEC-31-1998
JAN-01-1998
DEC-31-1998
27,618
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(42,983)
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(42,983)
0
0
0
(42,983)
(1.60)
(1.60)