AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON FEBRUARY 5, 1999
REGISTRATION NO. 333-_____

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

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. [ ]

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered	Proposed maximum offering price per share(1)	Proposed maximum aggregate offering price	Amount of registration fee
Common Stock, $.001 per share	4,000,000	$13.25	$53,000,000	$14,734

(1) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(c) of the Securities Act of 1933 based upon the average of the high and low prices of the Registrant's Common Stock as reported on the Nasdaq National Market on February 3, 1999.

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 5, 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.

Isis Pharmaceuticals is a trademark of the Company. 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.

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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

We believe we have enough money to satisfy our 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 book value of the Company at September 30, 1998 was $2,211,000 or approximately $.08 per share of Common Stock. Net tangible book value per share represents the amount of the Company's tangible assets less total liabilities, divided by 26,879,000 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 September 30, 1998 would have been $53,111,000 or $1.72 per share, an immediate increase in net tangible book value of $1.64 per share to existing stockholders and an immediate dilution in net tangible book value of $11.03 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 September 30, 1998	$ .08	
Increase per share attributable to new investors	$1.64	
Pro forma net tangible book value per share after offering		$ 1.72
Net tangible book value dilution per share to new investors		$11.03

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

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, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the reports of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given upon the authority of such firm as experts in accounting and auditing.

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 it 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 omission 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.

(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 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 5th 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 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 5, 1999
/s/ B. Lynne Parshall B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	February 5, 1999
/s/ Alan C. Mendelson Alan C. Mendelson	Director	February 5, 1999
/s/ Christopher F.O. Gabrieli Christopher F.O. Gabrieli	Director	February 5, 1999
/s/ William R. Miller William R. Miller	Director	February 5, 1999
/s/ Mark B. Skaletsky Mark B. Skaletsky	Director	February 5, 1999
/s/ Larry Soll Larry Soll, Ph.D.	Director	February 5, 1999
/s/ Joseph H. Wender Joseph H. Wender	Director	February 5, 1999
Burkhard Blank	Director	February , 1999

EXHIBIT INDEX

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24.1	Power of Attorney. Reference is made to page II-5.	

(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, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3), and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of its common stock, to be filed with the Securities and Exchange Commission on February 5, 1999, and to the incorporation by reference therein of our report dated January 23, 1998, with respect to the financial statements and schedules 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.

/s/ ERNST & YOUNG LLP

San Diego, California
February 5, 1999