AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON MAY 10, 1999

REGISTRATION NO. 333-71911

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 3

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, SUITE 1100
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. [X]

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.

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THE INFORMATION CONTAINED IN THIS PROSPECTUS IS NOT COMPLETE AND MAY BE CHANGED. THESE SECURITIES MAY NOT BE SOLD TO YOU 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.

SUBJECT TO COMPLETION, DATED MAY 10, 1999

PROSPECTUS

4,000,000 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

This prospectus will allow us to issue common stock over time. This means:

- we may issue the shares offered in this prospectus from time to time;

- we will provide a prospectus supplement each time we issue common stock;

- the prospectus supplement will inform you about the specific terms of that offering and also may add, update or change information contained in this document; and

- you should read this document and any prospectus supplement carefully before you invest.

Isis' common stock is traded on the Nasdaq National Market under the symbol "ISIP". On April 30, 1999, the last reported sale price for our common stock on the Nasdaq National Market was $10.4375 per share.

INVESTING IN OUR COMMON STOCK INVOLVES CERTAIN RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 5.

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.

The date of this prospectus is , 1999

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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 company. Dr. Debby Jo Blank joined Isis 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 Isis' manufacturing and regulatory affairs activities in addition to her previous responsibilities.

THE OFFERING

Common stock offered in this prospectus.....	4,000,000 shares
Common stock outstanding after the offering.....	32,240,000 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 April 28, 1999. Does not include 7,862,157 shares of common stock issuable upon exercise of outstanding options or 1,015,000 shares of common stock issuable upon exercise of outstanding warrants as of April 28, 1999.

RISK FACTORS

Please consider the following risk factors carefully in addition to the other information contained in this prospectus and in any other documents incorporated by reference into this prospectus from our other SEC filings.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN REGULATORY APPROVAL FOR OUR PRODUCTS.

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration regulations, to show the safety and efficacy of each of our drug candidates, as well as its optimum dosage, before the FDA can approve a drug candidate for sale. We cannot guarantee that we will be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our products under development. Delays in receiving these approvals, failure by us or our partners to receive these approvals at all or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

While limited trials of our products have to date produced favorable results, significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products. We expect to have ongoing discussions with the FDA and foreign regulatory agencies with respect to all of our drugs in clinical development.

OUR BUSINESS WILL SUFFER IF OUR PRODUCTS ARE NOT USED BY DOCTORS TO TREAT PATIENTS.

We cannot guarantee that any of our products in development, if approved for marketing, will be used by doctors to treat patients. We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. We delivered our first commercial shipment of Vitravene to our partner CIBA Vision in 1998, earning product revenue of $560,000.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals,
- the establishment and demonstration in the medical and patient community of the clinical efficacy and safety of our product candidates and their potential advantages over competitive products, and
- reimbursement policies of government and third-party payors.

In addition, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will accept and use any products that we may develop.

OUR BUSINESS WILL SUFFER IF ANY OF OUR COLLABORATIVE PARTNERS FAIL TO DEVELOP, FUND OR SELL ANY OF OUR PRODUCTS UNDER DEVELOPMENT.

If any collaborative partner fails to develop or sell any product in which we have rights, our business may be negatively affected. While we believe that

our collaborative

partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in commercialized products. The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program.

Collaborative partners may be pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs.

We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful.

OUR BUSINESS COULD SUFFER IF THE RESULTS OF FURTHER CLINICAL TESTING INDICATE THAT ANY OF OUR PRODUCTS UNDER DEVELOPMENT ARE NOT SUITABLE FOR COMMERCIAL USE.

Drug discovery and development involves inherent risks, including the risk that molecular targets prove unsuccessful and the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings or have undesirable side effects. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development of drug candidates based upon antisense technology, a novel drug discovery tool in designing drugs that work at the genetic level to block the production of disease-causing proteins.

WE HAVE INCURRED LOSSES AND OUR BUSINESS WILL SUFFER IF WE FAIL TO ACHIEVE PROFITABILITY IN THE FUTURE.

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since Isis was founded in January 1989. As of December 31, 1998, our accumulated losses were approximately $197 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential relative to most pharmaceutical products. We expect to incur additional operating losses over the next several years and we expect losses to increase as our preclinical testing and clinical trial efforts continue to expand. We cannot guarantee that we will successfully develop, receive regulatory approval for, commercialize, manufacture, market or sell any additional products, or achieve or sustain future profitability.

OUR BUSINESS WILL SUFFER IF WE FAIL TO OBTAIN TIMELY FUNDING.

Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the proceeds of this offering and interest earned thereon, will be adequate to satisfy our capital needs until at least the end of 2000.

We expect that we will need substantial additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- the market acceptance of Vitravene;
- the costs involved in filing, prosecuting and enforcing patent claims;
- competing technological and market developments, including the introduction of new therapies that address our markets; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we are unable to raise the total amount of proceeds covered by this prospectus, we will need to raise additional funds to finance our research and development and other operating activities. If we find that we do not have enough money, additional funds may be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

OUR BUSINESS WILL SUFFER IF WE CANNOT MANUFACTURE OUR PRODUCTS OR HAVE A THIRD PARTY MANUFACTURE OUR PRODUCTS AT LOW COSTS SO AS TO ENABLE US TO CHARGE COMPETITIVE PRICES TO BUYERS.

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

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

OUR BUSINESS WILL SUFFER IF WE FAIL TO COMPETE EFFECTIVELY WITH OUR COMPETITORS.

Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing other new therapeutic drug candidates that are more effective than any drug candidates that we have been developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time to recover our research, development or commercialization expenses.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

OUR BUSINESS WILL SUFFER IF WE ARE UNABLE TO PROTECT OUR PATENTS OR OUR PROPRIETARY RIGHTS.

Our success depends to a significant degree upon our ability to develop proprietary products. However, we cannot assure you that patents will be granted on any of our patent applications in the United States or in other countries. We also cannot assure you that the scope of any of our issued patents will be sufficiently broad to offer meaningful protection. In addition, our issued patents or patents licensed to us could be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

INTELLECTUAL PROPERTY LITIGATION COULD HARM OUR BUSINESS.

We have not experienced any patent or other intellectual property litigation. However, we cannot guarantee that we will not have to defend our intellectual property rights in the future. In the event of an intellectual property dispute, we may be forced to litigate or otherwise defend our intellectual property assets. Such disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and such expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claimed an intellectual property right to technology we use, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. Although we might under these circumstances attempt to obtain a license to such intellectual property, we may not be able to do so on favorable terms, if at all.

THE LOSS OF KEY PERSONNEL, OR THE INABILITY TO ATTRACT AND RETAIN HIGHLY SKILLED PERSONNEL, COULD ADVERSELY AFFECT OUR BUSINESS.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. Recently, Dr. Daniel Kisner, our President and Chief Operating Officer and director resigned all positions to assume the position of Chief Executive Officer of Caliper Technologies, a privately held company. Dr. Kisner's resignation is not expected to have a material adverse effect on our business. It is also critical to our success to recruit and retain qualified scientific personnel to perform research and development work. Although we believe we will be successful in attracting and keeping skilled and experienced scientific personnel, we may not be able to do so on acceptable terms, because of stiff competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

OUR STOCK PRICE MAY CONTINUE TO BE HIGHLY VOLATILE.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. During the last twelve months, the market price of our common stock has ranged from $7 to $16. The market price can be affected by many factors, including, for example, fluctuation in our operating results, announcements of technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

PROVISIONS IN OUR CERTIFICATE OF INCORPORATION AND DELAWARE LAW MAY PREVENT STOCKHOLDERS FROM RECEIVING A PREMIUM FOR THEIR SHARES.

Our certificate of incorporation provides for classified terms for the members of the board of directors. Our certificate also includes a provision that requires at least 66 2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, 15% or more of our voting stockholders, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

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

WHERE YOU CAN GET MORE INFORMATION

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference rooms in Washington, D.C., New York, NY and Chicago, IL. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. Our SEC filings are also available at the SEC's Web site at "http://www.sec.gov". In addition, you can read and copy our SEC filings at the office of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006.

The SEC allows us to "incorporate by reference" information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934:

- Annual Report on Form 10-K for the year ended December 31, 1998;

- Proxy Statement for the 1999 Annual Meeting of Stockholders;

- Current Report on Form 8-K dated as of April 20, 1999; and

- Isis' registration statement on Form 8-A filed on April 2, 1991, which includes a description of our common stock.

You may request a copy of these filings at no cost, by writing or telephoning us at the following address or telephone number:

Isis Pharmaceuticals, Inc.
Attn: Vice President of Finance
2292 Faraday Avenue
Carlsbad, CA 92008
Telephone Number (760) 931-9200

This prospectus is part of a larger registration statement we filed with the SEC. You should rely only on the information incorporated by reference or provided in this prospectus. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front of the document.

USE OF PROCEEDS

We cannot guarantee that we will receive any proceeds in connection with this offering.

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

We intend to use the net proceeds of this offering, if any, for our 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. We have not identified precisely the amounts we plan to spend on each research, drug discovery and development program or the timing of such expenditures. Isis, however, currently plans that the proceeds, if any, will be used for product development, including clinical trials, preclinical studies, manufacturing scale-up and facilities and equipment acquisition. The remaining proceeds, if any, 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 amount and timing of the proceeds from this offering, progress of our 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 our 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 our operations, including the acquisition of tenant improvements and capital equipment, such as mortgage or lease financing, may be used by us 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 our current operating plan, we believe that our available cash and existing sources of revenue and 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.

Proceeds of this offering, if any, may also be used to acquire companies or products that complement the business of Isis. We are not planning or negotiating any such transactions as of the date of this prospectus.

DILUTION

The net tangible deficit of Isis 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 our 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 $10.44 per share and the application of the estimated net proceeds therefrom (after deducting estimated offering expenses) the pro forma net tangible book value of Isis as of December 31, 1998 would have been $27,364,000 or $0.88 per share, an immediate increase in net tangible book value of $1.41 per share to existing stockholders and an immediate dilution in net tangible book value of $9.62 per share to purchasers of common stock in the offering, as illustrated in the following table:

Assumed public offering price per share.....		$10.44
Net tangible book value per share at December 31, 1998.....	$(.53)	
Increase per share attributable to new investors.....	$1.41	
Pro forma net tangible book value per share after offering.....		$ .88
Net tangible book value dilution per share to new investors.....		$ 9.62

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 Isis' 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
Write-off of acquired patents	5,238	--	--
General and administrative	9,511	8,078	6,246
Total operating expenses	76,949	64,018	51,899
Loss from operations	(37,778)	(31,296)	(29,236)
Interest income	4,150	3,815	3,921
Interest expense	9,355	3,585	1,206
Net loss	$(42,983)	$(31,066)	$(26,521)
Basic and diluted net loss per share	$ (1.60)	$ (1.17)	$ (1.04)
Shares used in computing basic and diluted net loss per share	26,873	26,456	25,585

	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 our business and products and their projected prospects and qualities, and our relationships with our corporate partners. Such statements are subject to 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 these 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, 1998 which is on file with the U.S. Securities and Exchange Commission, a copy of which is available from us.

Since our inception in January 1989, almost all of our resources have been devoted to our research, drug discovery and drug development programs. We are not yet profitable and expect to continue to have operating losses for the next several years. 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 we are able to fund and offsets a portion of our research and development costs. See Item 1, "Business -- Collaborative Agreements." In 1998, Isis received approval from the FDA to begin marketing our first product, Vitravene, a drug used to treat CMV retinitis.

RESULTS OF OPERATIONS

YEARS ENDED DECEMBER 31, 1998 AND DECEMBER 31, 1997

Our revenue from collaborative research and development agreements was $38.6 million for the year ended December 31, 1998 compared with $32.7 million in 1997, an increase of 18%. The receipt of $5 million from CpG ImmunoPharmaceuticals, Inc. for a license to certain issued patents together with $1.8 million from a research collaboration with Merck contributed to this revenue increase. 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 patents. This expense arises from the 1998 acquisition of the antisense patent estate from Gilead Sciences, Inc. The acquired patents and patent applications cover a broad array of proprietary antisense chemistry and drug delivery systems. We purchased Gilead's patent estate to consolidate and supplement our dominant proprietary position in antisense technology. The cost of these acquired patents was written off in accordance with our accounting policies as described in Note 1. 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.

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

At December 31, 1998, our net operating loss carryforward for federal income tax purposes was approximately $193.5 million. The net operating loss and research credit carryforwards make up a majority of our deferred tax assets. We will only be able to use the net operating loss and research credits, and realize the benefit of these deferred tax assets, if we become profitable. We have fully reserved all of our deferred tax assets as their realization is uncertain. Our research credit carryforward for federal income tax purposes was approximately $8.4 million. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods, due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that this limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may or may not be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

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

YEARS ENDED DECEMBER 31, 1997, AND DECEMBER 31, 1996

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

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

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

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

LIQUIDITY AND CAPITAL RESOURCES

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

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

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

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

As of December 31, 1998, our long-term obligations totaled $81.3 million compared to $58.7 million at December 31, 1997. This increase was due to the $15 million follow-on debt financing together with the accrual of interest on the ten-year notes described above. Additional capital lease financing to fund equipment acquisitions also contributed to the

increase. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease lines as long as the terms continue to remain commercially attractive. We believe that our existing cash, cash equivalents, short-term investments, combined with interest income and contract revenue and the proceeds of this offering and interest earned thereon will be sufficient to meet our capital needs until at least the end of 2000.

YEAR 2000 COMPUTER ISSUES

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

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

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

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

Our most likely exposure to Year 2000 problems is related to our high dependence on commercial utilities such as water and power. If the providers of these utilities are not able

to maintain service due to Year 2000 noncompliance it could result in temporarily halting research and development activities until the service is restored or until suitable alternate facilities in a different geographic area could be obtained. It is not possible to precisely estimate the length of delays in research and development projects in those circumstances, but it could range from three to six months.

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

\ PLAN OF DISTRIBUTION

We may offer the common stock:

- directly to purchasers;

- to or through underwriters;

- through dealers, agents or institutional investors; or

- through a combination of such methods.

Regardless of the method used to sell the common stock, we will provide a prospectus supplement that will disclose:

- the identity of any underwriters, dealers, agents or investors who purchase the common stock;

- the material terms of the distribution, including the number of shares sold and the consideration paid;

- the amount of any compensation, discounts or commissions to be received by the underwriters, dealers or agents;

- the terms of any identification provisions, including indemnification from liabilities under the federal securities laws; and

- the nature of any transaction by an underwriter, dealer or agent during the offering that is intended to stabilize or maintain the market price of the common stock.

LEGAL MATTERS

The validity of the issuance of the common stock offered in this prospectus

will be passed upon for Isis by Grantland E. Bryce, Vice President and General Counsel of Isis. 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, 1998, have been audited by Ernst & Young LLP, independent auditors, as set forth in their report. We incorporate by reference their report as a part of this prospectus. Such financial statements are incorporated into this prospectus in reliance upon the reports of Ernst & Young LLP given upon the authority of Ernst & Young LLP 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 Isis' 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)

	DECEMBER 31,	
	1998	1997
ASSETS		
Current assets:		
Cash and cash equivalents	$ 27,618	$ 38,102
Short-term investments	31,230	48,684
Contracts receivable	3,466	289
Prepaids and other current assets	873	2,075
Total current assets	63,187	89,150
Property, plant and equipment, net	21,542	18,785
Patent costs, net	9,113	7,485
Deposits and other assets	2,232	2,461
	$ 96,074	$117,881
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 2,977	$ 2,843
Accrued payroll and related expenses	3,088	2,242
Accrued liabilities	2,714	4,347
Deferred contract revenues	10,176	14,893
Current portion of long-term obligations	3,581	2,252
Total current liabilities	22,536	26,577
Long-term obligations, less current portion	77,724	56,452
Commitments (See Note 3)		
Stockholders' equity (deficit):		
Common stock, $.001 par value; 50,000,000 shares authorized, 27,053,000 shares and 26,655,000 shares issued and outstanding at December 31, 1998 and 1997, respectively	27	27
Additional paid-in capital	192,737	188,793
Accumulated Other Comprehensive Income	166	165
Accumulated deficit	(197,116)	(154,133)
Total stockholders' equity (deficit)	(4,186)	34,852
	$ 96,074	$117,881

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

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

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

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

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1998

1. ORGANIZATION AND SIGNIFICANT ACCOUNTING POLICIES

Organization and business activity -- Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, Isis was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc., in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

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

Contract revenues and expenses -- Contract revenues consist of non-refundable research and development funding and are recorded as earned based on the performance requirements of the collaborative research and development contracts. Contract fees for which no further performance obligations exist are recognized when the payments are received or when the collection is assured. Payments received in excess of amounts earned are recorded as deferred contract revenues. Research and development costs are expensed as incurred. For the years ended December 31, 1998, 1997 and 1996, costs and expenses of approximately $35,000,000, $31,000,000, and $29,000,000 respectively, were related to collaborative research and development arrangements.

Revenue recognition -- Isis recognizes revenue from product sales at the time of shipment. An estimate is made of the amount of the product that may be returned and current period sales are reduced accordingly. License fees consist of non-refundable fees from the sale of license rights to our proprietary technologies. Revenue from these fees is recorded when no further performance obligations exist.

Cash equivalents and short-term investments -- Cash equivalents and short-term investments consist of highly liquid debt instruments. Isis considers instruments with original maturities of less than 90 days to be cash equivalents. Isis has recorded its cash equivalents and short-term investments at fair market value as of December 31, 1998, and has classified all of its investments as available-for-sale. This category includes all securities which Isis does not have the positive intent and ability to hold to maturity. The measurement basis for available-for-sale securities is fair market value. Unrealized gains and losses, net of the related tax effect, are included in Accumulated Other Comprehensive Income, a separate component of stockholders' equity. See Note 2 -- Investments.

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

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

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

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

Patent costs -- Isis capitalizes certain costs related to patent applications, principally consisting of legal and filing fees. These costs are regularly reviewed to determine that they include costs for patent applications Isis is pursuing. Costs related to applications that are not being actively pursued are evaluated under Accounting Principles Board Statement 17: Intangible Assets and are adjusted to an appropriate amortization period which results in an immediate write-off. Accumulated patent costs are amortized on a straight-line basis over their estimated economic lives of approximately 10 years, beginning with the date the patents are issued. The weighted average remaining life of issued patents is 8.2 years. Accumulated amortization was $493,000 at December 31, 1998 and $240,000 at December 31, 1997.

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

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

Comprehensive income -- Isis adopted Statement of Financial Accounting Standards (FAS) 130, "Reporting Comprehensive Income", at December 31, 1998. Under FAS 130, Isis is required to display comprehensive income and its components as part of Isis' full set

of financial statements. The measurement and presentation of net income did not change. Comprehensive income is comprised of net income and certain changes in equity that are excluded from net income. Specifically, FAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which were reported separately in stockholders' equity, to be included in accumulated other comprehensive income. Comprehensive income for the years ended December 31, 1998, 1997 and 1996 have been reflected in the Consolidated Statement of Stockholders' Equity.

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

2. INVESTMENTS

Isis invests its excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends in yields and interest rates. Isis has not experienced any losses on its short-term investments. As of December 31, 1998, 79% of the debt securities held by Isis had a contractual maturity of one year or less, and the remaining 21% of the portfolio was due within 2 years.

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

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

3. LONG-TERM OBLIGATIONS AND COMMITMENTS

Isis obtained $25,060,000 in private debt financing during 1997 and an additional $15,000,000 in 1998. The terms of the financing provide for a 10 year maturity on the debt, interest of 14% per annum and deferred interest payments for the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan,

November 1, 2007. No principal repayments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $78 million on November 1, 2002. In conjunction with the debt financing, Isis issued warrants to the lender to purchase shares of common stock, exercisable at $25 per share. Isis issued warrants for 500,000 common shares in 1997 and 300,000 shares in 1998. The fair value of the warrants was estimated using the Black-Scholes option pricing model, with the following assumptions: expected life of 4.5 years, expected dividend yield of zero percent and expected volatility of 60 percent. The assumed risk free interest rate was 5.9 percent. The warrants were valued at $3,780,000 and $1,646,000 respectively, and were credited to equity. The allocation of value to the warrants creates an effective debt discount which is amortized using the effective interest method. The effective interest rate of this debt is approximately 16 percent, including the effect of the discount amortization. The debt is carried on the balance sheet net of the unamortized amount allocated to the warrants, and including accrued interest. The carrying amount at December 31, 1998 was $41,321,000. The fair value of this debt at December 31, 1998 approximated $45,000,000. The fair value of the long-term debt is estimated using discounted cash flow analyses, based on current borrowing rates for similar types of borrowing arrangements.

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

In 1996 and 1997, Isis borrowed a total of $22,576,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim International GmbH. The borrowed funds are being used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the 7 year U.S. interbanking rate plus 2.0%, determined at the time each advance is made. Interest payments are due twice each year with principal repayment due 7 years after the advance date. The principal may be repaid in cash or stock, at Isis' option. If Isis elects to repay the loan in shares of Isis common stock, repayment will be made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of December 31, 1998 was $22,576,000, which approximated fair value.

In December 1998, Isis purchased from Gilead Sciences, Inc. ("Gilead"), the holdings of its antisense patent estate. This acquisition includes patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. The purchase price was $6,000,000 payable in four installments over the next three years. Isis made the initial $2,000,000 payment in December 1998. Isis has recorded the net present value of the future payments, using an interest rate of 10%, as a

long-term obligation on the balance sheet. The balance of this obligation at December 31, 1998 was $3,238,000, which approximated fair value.

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

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

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

4. STOCKHOLDERS' EQUITY

Stock Option Plans and Other Employee Option Grants -- In June 1989, Isis adopted a stock option plan which provides for the issuance of incentive and non-qualified stock options for the purchase of up to 10,200,000 shares of common stock to its employees and certain other individuals. In addition to the options issued under the terms of the 1989 plan, non-qualified options to purchase 319,000 shares of common stock have been granted to certain employees. The plan also includes provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. Typically options expire 10 years from the date of grant. Options granted after December 31, 1995 vest over a 4 year period, with 25% exercisable at the end of 1 year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vest over a 5 year period. At December 31, 1998, a total of 4,347,000 shares were exercisable, and 1,903,000 were available for future grant.

In July 1992, Isis adopted the 1992 Non-Employee Directors' Stock Option Plan which provides for the issuance of non-qualified stock options for the purchase of up to

300,000 shares of common stock to its non-employee directors. Options under this plan expire 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in 4 equal annual installments beginning 1 year after the date of grant. Options granted before January 1, 1996 vest over a 5 year period. At December 31, 1998, 139,000 shares issued under this plan were exercisable and 58,000 Shares were available for future grant.

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

	NUMBER OF SHARES	PRICE PER SHARE	WEIGHTED AVERAGE PRICE/SHARE
Outstanding at December 31, 1995.....	5,446	$ .14 to $19.75	
Granted.....	1,337	11.38 to 20.00	
Exercised.....	(468)	.14 to 17.88	
Terminated.....	(222)	4.00 to 18.63	
Outstanding at December 31, 1996.....	6,093	$ .14 to $20.00	$ 8.48
Granted.....	1,071	13.19 to 19.88	
Exercised.....	(395)	.14 to 16.00	
Terminated.....	(327)	3.75 to 18.25	
Outstanding at December 31, 1997.....	6,442	$ .14 to $20.00	$ 9.80
Granted.....	1,168	7.06 to 15.44	
Exercised.....	(320)	.14 to 14.50	
Terminated.....	(304)	3.75 to 20.00	
Outstanding at December 31, 1998.....	6,986	$ .14 to $19.88	$10.27

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

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

Employee Stock Purchase Plan -- In 1991, the Board of Directors adopted the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance

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

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

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

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

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

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

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

5. INCOME TAXES

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

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

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

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

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

Annual use of Isis' net operating loss and credit carryforwards will be limited under the Internal Revenue Code as a result of cumulative changes in ownership of more than 50% during the periods ended December 31, 1989 and 1991. However, Isis believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. RESEARCH AND DEVELOPMENT COLLABORATIVE ARRANGEMENTS AND LICENSING AGREEMENTS

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

In July 1997, Isis and CIBA Vision Corporation entered into an agreement granting CIBA Vision exclusive worldwide distribution rights for Vitravene (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. At the inception of the agreement, CIBA Vision paid us a $5 million non-refundable pre-commercial fee to partially reimburse us for the costs incurred in discovering and developing Vitravene to that point. That payment was recognized as revenue in 1997 and included in the statement of operations as contract revenue. In August 1998, the FDA approved Vitravene 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 third quarter of 1998 and recorded $560,000 in net product revenues. Under the CIBA Vision agreement, Isis earned contract revenue of $7,500,000 in 1998 and $5,000,000 (which represents the pre-commercial fee described above) in 1997.

In July 1995, Isis and Boehringer Ingelheim International GmbH signed definitive agreements and completed the formation of a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28,500,000 in cash plus certain license rights. Of the $28,500,000, $21,300,000 was accounted for as equity and $7,200,000 was accounted for as deferred revenue, representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. In December 1996, coinciding with the achievement of a milestone, Boehringer Ingelheim purchased 409,000 shares for $10,000,000. Of that total, $6,000,000 was accounted for as equity and $4,000,000 as

deferred revenue. The agreement also provides that Boehringer Ingelheim is entitled to designate 1 person for election to Isis' Board of Directors. As of December 31, 1998 Boehringer Ingelheim owned approximately 9% of Isis' outstanding common stock. Boehringer Ingelheim and Isis are providing equal funding for the combined research and development program and will share equally in the profits from all products of the collaboration. Boehringer Ingelheim has also provided Isis with a $40,000,000 line of credit, available under certain circumstances to be used in support of the combined programs. As of December 31, 1998, the outstanding balance under this line of credit was $22,576,000. The statement of operations for the years ended December 31, 1998, 1997 and 1996 reflects contract revenues of $6,544,000, $5,603,000 and $4,024,000, respectively, from this collaboration.

In June 1998, Isis entered into a research collaboration with Merck & Co. to discover small molecule drug candidates to treat patients infected with Hepatitis C virus ("HCV"). Isis and Merck will design, synthesize, and evaluate novel compounds that Merck will screen in its proprietary assays for identifying HCV replication inhibitors. Merck will commercialize drugs arising from the collaboration, and Isis retains the right to use technology developed in collaboration in our antisense program. The three year collaboration provides us with annual research support plus technology access fees, and milestone payments and royalties upon commercialization. In 1998, Isis received a total of $3,875,000 from Merck under the terms of this agreement.

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

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

In December 1998, we purchased from Gilead Sciences, Inc. the holdings of its antisense patent estate. This acquisition includes patents and patent applications covering a broad proprietary suite of antisense chemistry and antisense drug delivery systems. We acquired these patents and patent applications to consolidate and supplement our dominant proprietary position in antisense technology. The purchase price was $6,000,000 payable in four installments over the next three years. Isis made the initial $2,000,000 payment in December 1998. Isis has recorded the net present value of the future payments as a long-

term obligation on the balance sheet. The balance of this obligation at December 31, 1998 was $3,238,000. The cost of these acquired patents was written off in 1998 in accordance with our accounting policies as described in Note 1.

In December 1998, Isis entered into a collaborative research agreement with Zeneca Pharmaceuticals to discover, develop and commercialize novel antisense-based cancer drugs. Under the terms of this collaboration, Isis will create and, with Zeneca, screen antisense-based candidates for certain cancer targets. 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, Isis 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." Isis 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.

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all expenses payable by Isis 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, Isis 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.

Isis' 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 and (ii) require Isis 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. Isis 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 Isis, 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 Isis 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 Isis or its stockholders when the director was aware or should have been aware of a risk of serious injury to Isis 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 Isis or its stockholders, for improper transactions between the director and Isis 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 Isis 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 Isis 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 Isis and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth 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 Isis as to which indemnification is being sought, nor is Isis aware of any threatened litigation that may result in claims for indemnification by any officer or director.

Isis has an insurance policy covering the officers and directors of Isis 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)
4.3	Certificate of Designation of the Series A Convertible Preferred Stock
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.*
99.1	Form of Confidentiality Agreement.

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

* Previously Filed

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:

(1) To file, during any period in which offers or sales are being made pursuant to this registration statement, a post-effective amendment to this registration statement to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment 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; and

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

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. 3 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 10th day of May, 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. 3 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)	May 10, 1999
* B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	May 10, 1999

SIGNATURES	TITLE	DATE
*	Director	May 10, 1999
Alan C. Mendelson		
*	Director	May 10, 1999
Christopher F.O. Gabrieli		
*	Director	May 10, 1999
William R. Miller		
*	Director	May 10, 1999
Mark B. Skaletsky		
*	Director	May 10, 1999
Larry Soll, Ph.D.		
*	Director	May 10, 1999
Joseph H. Wender		
	Director	May 10, 1999
Burkhard Blank		

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.

* Previously Filed.

EXHIBIT 4.3

CERTIFICATE OF DESIGNATION
OF THE
SERIES A CONVERTIBLE PREFERRED STOCK
(PAR VALUE $.001 PER SHARE)
OF
ISIS PHARMACEUTICALS, INC.

PURSUANT TO SECTION 151 OF THE
GENERAL CORPORATION LAW OF THE STATE OF DELAWARE

ISIS PHARMACEUTICALS, INC., a company organized and existing under the General Corporation Law of the State of Delaware (the "Company"), in accordance with the provisions of Section 103 thereof, and pursuant to Section 151 thereof, DOES HEREBY CERTIFY:

That the Restated Certificate of Incorporation of the Company (the "Restated Certificate") authorizes the creation of up to 15,000,000 shares of the Company's preferred stock, par value $.001 per share (such preferred stock, together with all other preferred stock of the Company the creation of which is in the future authorized by the Restated Certificate, referred to herein as the "Preferred Stock"); and

That pursuant to the authority conferred upon the Board of Directors (the "Board") by the Restated Certificate, the Board on February 26, 1999, approved the creation, issuance and the voting powers of shares of Preferred Stock to be issued in one series and adopted the following resolution creating a series of 120,150 shares of Preferred Stock designated as set forth below:

RESOLVED, that pursuant to the authority expressly granted to and vested in the Board by provisions of the Restated Certificate of the Company and the General Corporation Law of the State of Delaware, the issuance of a series of Preferred Stock, which shall consist of 120,150 shares of the 15,000,000 shares of Preferred Stock which the Company now has authority to issue, be, and the same hereby is, authorized, and the Board hereby fixes the powers, designations, preferences and relative participating, optional or other special rights, and the qualifications, limitations or restrictions thereof, of the shares of such series (in addition to the powers, designations, preferences and relative participating, optional or other special rights, and the qualifications, limitations or restrictions thereof, set forth in the Restated Certificate which may be applicable to the Preferred Stock) authorized by this resolution as follows:

SECTION 1. DESIGNATION OF SERIES A PREFERRED STOCK. The designation of such series of Preferred Stock authorized by this resolution shall be Series A Convertible Preferred Stock (the "Series A Preferred"). The Series A Preferred is issuable solely in whole shares that shall entitle the holder thereof to participate in the distributions and to have the benefit of all other rights of holders of Series A Preferred, as set forth herein and in the Restated Certificate.

SECTION 2. DIVIDEND RIGHTS OF SERIES A PREFERRED.

(a) When and if the Board shall declare a dividend or distribution payable with respect to the then-outstanding shares of Common Stock of the Company, other than any such dividend or distribution payable in shares of Common Stock or other securities of the Company (which is provided for in Sections 4(f) and (g)), the holders of the Series A Preferred shall be entitled to the amount of dividends per share that would be payable on the largest number of whole shares of Common Stock into which a holder's aggregate shares of Series A Preferred could then be converted pursuant to Section 4(a) hereof without regard to the provisions of Section 5 (such number to be determined as of the record date for the determination of holders of Common Stock entitled to receive such dividend, and, if the record date is prior to March 31, 2002, for purposes of determining the number of shares of Common Stock into which the Series A Preferred could then be converted, the Series A Conversion Price will be calculated in accordance with Section 4(c)(i) for the 60 trading days ending two business days prior to the record date).

(b) In addition to Section 2(a) above, the Series A Preferred shall be entitled to a mandatory dividend equal to 5.0% per year of $100 per share (the "Series A Original Issue Price") (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares) plus accrued dividends thereon, compounded on a semi-annual basis. Such dividend shall be payable solely by the issuance of additional shares of Common Stock upon conversion of the Series A Preferred into Common Stock pursuant to Section 4 hereof; provided that, in the event the Company exercises the Redemption Right (as defined in Section 5(c)), such dividend shall be payable in cash upon such redemption in accordance with Section 5. The dividend to be paid to a holder under this Section 2(b) upon a conversion of the Series A Preferred shall be equal to that number of shares Common Stock determined by dividing the total dividend accrued with respect such holder's Series A Preferred by the Series A Conversion Price, determined in accordance with Section 4(c) hereof, then in effect. No dividends shall be payable under this Section 2(b) in the event the Exchange Right is exercised pursuant to Section 6.

SECTION 3. SENIORITY; LIQUIDATION PREFERENCE.

(a) The Series A Preferred shall rank senior to or pari passu with any future class or series of Preferred Stock issued by the Company and senior to the Company's Common Stock.

(b) In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company, other than a Significant Transaction (as defined below) (collectively, a "Liquidation"), the holders of Series A Preferred then outstanding shall be entitled to be paid, pro rata, out of the assets of the Company legally available for distribution to its stockholders, whether from capital, surplus or earnings, before any payment shall be made in respect of any other class or series of stock ranking junior to the Series A Preferred, an amount equal to the Series A Original Issue Price per share (as adjusted for any combinations, consolidations, stock distributions, stock dividends or other recapitalizations with respect to such shares) (the "Series A Liquidation Preference"). If, upon a Liquidation, the assets of the Company available for distribution to its stockholders shall be insufficient to pay the holders of the Series A Preferred the full Series A Liquidation Preference to which they shall be entitled as set forth

above, then the entire assets of the Company legally available for distribution shall be distributed pro rata among the holders of the Series A Preferred in proportion to the Series A Liquidation Preference each such holder would otherwise be entitled to receive. After setting apart or paying in full the Series A Liquidation Preference due the holders of the Series A Preferred, the holders of the Series A Preferred will not be entitled to any further participation in any distribution of the assets of the Company, and the entire remaining assets of the Company legally available for distribution, if any, shall be distributed among the holders of Common Stock in proportion to the shares of Common Stock then held by them.

SECTION 4. CONVERSION PRIVILEGES.

(a) RIGHTS OF CONVERSION. Subject to the other provisions of this Certificate of Designation, each share of Series A Preferred shall be convertible, without payment of any additional consideration by the holder thereof and at the option of such holder, into such number of fully paid and nonassessable shares of Common Stock as is determined by dividing the Series A Original Issue Price, plus accrued but unpaid cash dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series A Conversion Price (as defined below) in effect at the time of conversion, at any time and from time to time after March 31, 2002, at the office of the Company or any transfer agent for such stock.

(b) AUTOMATIC CONVERSION.

(i) In the event that a Significant Transaction (as defined below) occurs, then, in such event, without giving effect to any Series A Liquidation Preference, the Series A Preferred shall automatically, and without the requirement of further action by the Company or the holders, be converted into such number of fully paid and nonassessable shares of Common Stock determined by dividing the Series A Original Issue Price, plus accrued but unpaid dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series A Conversion Price then in effect. For purposes of this Certificate of Designation, "Significant Transaction" shall mean (A) a reorganization, merger or consolidation in which immediately after (by virtue of securities issued as consideration for such transaction) the former shareholders of the Company do not hold at least 50% of the voting power of the surviving or acquiring entity, (B) an acquisition of all outstanding capital stock of the Company, (C) a liquidation of the Company or a winding down of its business, or (D) a sale or other transfer of all or substantially all of the Company's assets, but shall not include (1) a commencement of any bankruptcy or insolvency proceedings, whether voluntary or involuntary, (2) a filing for reorganization or relief under bankruptcy law, (3) a consent to the appointment of a receiver, liquidator or trustee for the Company or its assets, (4) a making of a general assignment by the Company for the benefit of its creditors or (5) any other similar corporate action.

(ii) Subject to the provisions of Section 5, upon April 20, 2005, the Series A Preferred shall automatically, and without the requirement of further action by the Company or the holders, be converted into such number of fully paid and nonassessable shares of Common Stock determined by dividing the Series A Original Issue Price, plus accrued but unpaid dividends under Section 2(a) and accrued dividends under Section 2(b), by the Series A Conversion Price then in effect. Any shares of Series A Preferred that are not automatically converted into shares of the Company's Common Stock as a result of the provisions of Section 5

shall remain issued and outstanding unless converted pursuant to the provisions of Section 4(a) or redeemed pursuant to the provisions of Section 5.

(c) SERIES A CONVERSION PRICE. The price at which shares of Common Stock shall be deliverable upon conversion of Series A Preferred (the "Series A Conversion Price") (i) for purposes of Sections 4(a) and 4(b)(ii) shall be equal to 125% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to March 31, 2002, subject to adjustment as set forth below, and (ii) for purposes of Section 4(b)(i) shall be equal to (A) if prior to March 31, 2002, 120% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to the date of first public announcement of the Significant Transaction, or (B) if on or after March 31, 2002, 125% of the average closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) per share for the 60 trading days ending two business days prior to the date of first public announcement of the Significant Transaction.

(c) MECHANICS OF CONVERSION. Before any holder of Series A Preferred shall be entitled to convert the same into shares of Common Stock, such holder shall surrender the certificate or certificates thereof, duly endorsed, at the office of the Company or of any transfer agent for such stock, and shall give written notice to the Company at such office that such holder elects to convert the same and shall state therein the name or names in which such holder wishes the certificate or certificates for shares of Common Stock to be issued. The Company shall, as soon as practicable thereafter, issue and deliver at such office to such holder of Series A Preferred or its nominee or nominees, a certificate or certificates for the number of shares of Common Stock to which such holder shall be entitled as aforesaid, together with cash in lieu of any fractional shares. Such conversion shall be deemed to have been made immediately prior to the close of business on the date of surrender of the shares of Series A Preferred to be converted. The person or persons entitled to receive the shares of Common Stock issuable upon such conversion shall be treated for all purposes as the record holder or holders of such shares of Common Stock on such date.

(e) ADJUSTMENT FOR STOCK SPLITS AND COMBINATIONS. If the Company shall at any time or from time to time after the date that the first share of Series A Preferred is issued (the "Original Issue Date") effect a subdivision of the outstanding Common Stock without a corresponding subdivision of the Series A Preferred, the Series A Conversion Price in effect immediately before that subdivision shall be proportionately decreased. Conversely, if the Company shall at any time or from time to time after the Original Issue Date combine the outstanding shares of Common Stock into a smaller number of shares without a corresponding combination of the Series A Preferred, the Series A Conversion Price in effect immediately before the combination shall be proportionately increased. Any adjustment under this Section 4(e) shall become effective at the close of business on the date the subdivision or combination becomes effective.

(f) ADJUSTMENT FOR COMMON STOCK DIVIDENDS AND DISTRIBUTIONS. If the Company at any time or from time to time after the Original Issue Date makes, or fixes a record date for the determination of holders of Common Stock entitled to receive, a dividend or other distribution payable in additional shares of Common Stock, in each such event the Series A Conversion Price that is then in effect shall be decreased as of the time of such issuance or, in the event such record date is fixed, as of the close of business on such record date, by multiplying the Series A Conversion Price then in effect by a fraction (i) the numerator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date, and (ii) the denominator of which is the total number of shares of Common Stock issued and outstanding immediately prior to the time of such issuance or the close of business on such record date plus the number of shares of Common Stock issuable in payment of such dividend or distribution; provided, however, that if such record date is fixed and such dividend is not fully paid or if such distribution is not fully made on the date fixed therefor, the Series A Conversion Price shall be recomputed accordingly as of the close of business on such record date and thereafter the Series A Conversion Price shall be adjusted pursuant to this Section 4(f) to reflect the actual payment of such dividend or distribution.

(g) ADJUSTMENTS FOR OTHER DIVIDENDS AND DISTRIBUTIONS. If the Company at any time or from time to time after the Original Issue Date makes, or fixes a record date for the determination of holders of Common Stock entitled to receive, a dividend or other distribution payable in securities of the Company other than shares of Common Stock, in each such event provision shall be made so that the holders of the Series A Preferred shall receive upon conversion thereof, in addition to the number of shares of Common Stock receivable thereupon, the amount of other securities of the Company which they would have received had their Series A Preferred been converted into Common Stock on the date of such event and had they thereafter, during the period from the date of such event to and including the conversion date, retained such securities receivable by them as aforesaid during such period, subject to all other adjustments called for during such period under this Section 4 with respect to the rights of the holders of the Series A Preferred or with respect to such other securities by their terms.

(h) ADJUSTMENT FOR RECLASSIFICATION, EXCHANGE AND SUBSTITUTION. If at any time or from time to time after the Original Issue Date, the Common Stock issuable upon the conversion of the Series A Preferred is changed into the same or a different number of shares of any class or classes of stock, whether by recapitalization, reclassification or otherwise (other than a subdivision or combination of shares or stock dividend or a reorganization, merger, consolidation or sale of assets provided for elsewhere in this Section 4), in any such event each holder of Series A Preferred shall have the right thereafter to convert such stock into the kind and amount of stock and other securities and property receivable upon such recapitalization, reclassification or other change by holders of the maximum number of shares of Common Stock into which such shares of Series A Preferred could have been converted immediately prior to such recapitalization, reclassification or change, all subject to further adjustment as provided herein or with respect to such other securities or property by the terms thereof.

(i) REORGANIZATIONS, MERGERS, CONSOLIDATIONS OR SALES OF ASSETS. If at any time or from time to time after the Original Issue Date, there is a capital reorganization of the Common Stock (other than a Signification Transaction or a subdivision or combination of shares or stock

dividend or a reorganization, merger, consolidation or sale of assets provided for elsewhere in this Section 4), as a part of such capital reorganization, provision shall be made so that the holders of the Series A Preferred shall thereafter be entitled to receive upon conversion of the Series A Preferred the number of shares of stock or other securities or property of the Company to which a holder of the number of shares of Common Stock deliverable upon conversion would have been entitled on such capital reorganization, subject to adjustment in respect of such stock or securities by the terms thereof. In any such case, appropriate adjustment shall be made in the application of the provisions of this Section 4 with respect to the rights of the holders of Series A Preferred after the capital reorganization to the end that the provisions of this Section 4 (including adjustment of the Series A Conversion Price then in effect and the number of shares issuable upon conversion of the Series A Preferred) shall be applicable after that event and be as nearly equivalent as practicable.

(j) CERTIFICATES AS TO ADJUSTMENTS. Upon the occurrence of each adjustment or readjustment of the number of shares of Common Stock issuable upon conversion of a share of Series A Preferred pursuant to this Section 4, the Company at its expense shall promptly compute such adjustment or readjustment in accordance with the terms hereof and prepare and furnish to each holder of Series A Preferred a certificate setting forth such adjustment or readjustment and showing in detail the facts upon which such adjustment or readjustment is based. The Company shall, upon the written request at any time of any holder of Series A Preferred, furnish or cause to be furnished to such holder a like certificate prepared by the Company setting forth (i) such adjustments and readjustments, (ii) the Series A Conversion Price at the time in effect, and (iii) the number of shares of Common Stock and the amount, if any, of other property which at the time would be received upon the conversion of the Series A Preferred.

(k) NOTICES OF RECORD DATE. In the event of any taking by the Company of a record of the holders of any class of securities for the purpose of determining the holders thereof who are entitled to receive any dividend (other than a cash dividend) or other distribution, any security or right convertible into or entitling the holder thereof to receive additional shares of Common Stock, or any right to subscribe for, purchase or otherwise acquire any shares of stock of any class or any other securities or property, or to receive any other right, the Company shall mail to each holder of Series A Preferred at least 10 days prior to the date specified therein, a notice specifying the date on which any such record is to be taken for the purpose of such dividend, distribution, security or right, and the amount and character of such dividend, distribution, security or right.

(l) ISSUE TAXES. The holders of Series A Preferred shall pay any and all issue, transfer and other taxes that may be payable in respect of any issue or delivery of shares of Common Stock on conversion of shares of Series A Preferred pursuant hereto.

(m) RESERVATION OF STOCK ISSUABLE UPON CONVERSION. The Company shall at all times reserve and keep available out of its authorized but unissued shares of Common Stock, solely for the purpose of effecting the conversion of the shares of the Series A Preferred, such number of its shares of Common Stock as shall from time to time be sufficient to effect the conversion of all outstanding shares of the Series A Preferred; and if at any time the number of authorized but unissued shares of Common Stock shall not be sufficient to effect the conversion

of all then outstanding shares of the Series A Preferred, the Company will take such corporate action as may, in the opinion of its counsel, be necessary to increase its authorized but unissued shares of Common Stock to such number of shares as shall be sufficient for such purpose, including, without limitation, engaging in best efforts to obtain the requisite stockholder approval of any necessary amendment to the Restated Certificate. All shares of Common Stock which are issuable upon such conversion shall, when issued, be duly and legally issued, fully paid and nonassessable and free of all taxes, liens and charges.

(n) FRACTIONAL SHARES. No fractional share shall be issued upon the conversion of any share or shares of Series A Preferred. All shares of Common Stock (including fractions thereof) issuable upon conversion of more than one share of Series A Preferred by a holder thereof shall be aggregated for purposes of determining whether the conversion would result in the issuance of any fractional share. If, after the aforementioned aggregation, the conversion would result in the issuance of a fraction of a share of Common Stock, the Company shall, in lieu of issuing any fractional share, pay the holder otherwise entitled to such fraction a sum in cash equal to the closing price of the Company's Common Stock on the Nasdaq National Market (or any other national securities exchange on which the Common Stock is then traded) on the day immediately preceding the conversion.

(o) NOTICES. Any notice required by the provisions of this Section 4 shall be in writing and shall be deemed effectively given: (i) upon personal delivery to the party to be notified, (ii) when telephonically confirmed if sent by telex or facsimile, (iii) five days after having been sent by registered or certified mail, return receipt requested, postage prepaid, or (iv) one day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. All notices shall be addressed to each holder of record at the address of such holder appearing on the books of the Company.

SECTION 5. LIMITATION ON ISSUANCE OF SHARES UPON CONVERSION; REDEMPTION.

(a) The following definitions shall apply to this Certificate of Designation:

(i) "Maximum Share Amount" shall mean the number of shares of the Company's Common Stock equal to 19.99% of the Company's Common Stock then outstanding;

(ii) "Excess Shares" shall mean Common Stock of the Company which, upon issuance, results in the beneficial ownership (as defined in Rule 13(d)-3 of the Securities Exchange Act of 1934) by a holder of shares of Common Stock in excess of the Maximum Share Amount;

(iii) "Exchange Rules" shall mean the rules or regulations of Nasdaq or any other principal securities market upon which the Common Stock of the Company is or becomes traded.

(b) Except as provided in Section 5(c) hereof, the Company shall not be obligated to issue upon conversion of the Series A Preferred, in the aggregate, Excess Shares if such issuance in excess of the Maximum Shares Amount would constitute a breach a breach or violation of the Company's obligations under the Exchange Rules.

(c) To the extent the Company will be required, or it appears likely to the Board of Directors of the Company that the Company will be required, to issue any Excess Shares, the Company shall promptly use its best efforts to obtain stockholder approval in accordance with Delaware law, the applicable rules of the Securities and Exchange Commission and the Exchange Rules. In the event the Company does not obtain stockholder approval, the Company shall have the right, at its option (the "Redemption Right"), to redeem, out of funds legally available therefor, all or any part of the Excess Shares at a redemption price, payable in cash, equal to the Series A Original Issue Price per share together with accrued and unpaid dividends on any such shares that are redeemed (the "Redemption Price"). The Company may exercise the Redemption Right by providing notice by mail, first class postage prepaid, to each holder of Series A Preferred of record (at the close of business on the business day preceding the day on which notice is given) of the Series A Preferred to be redeemed, at the address last shown on the records of the Company for such holder, notifying such holder of the redemption to be effected, specifying the number of shares to be redeemed from such holder, the date that the redemption is to occur (the "Redemption Date"), the place at which payment may be obtained and calling upon such holder to surrender to the Company, in the manner and at the place designated, such holder's certificate or certificates representing the shares to be redeemed (the "Redemption Notice"). On or after the Redemption Date, each holder of Series A Preferred to be redeemed shall surrender to the Company the certificate or certificates representing such shares in the manner and at the place designated in the Redemption Notice, and thereupon the Redemption Price of such shares shall be payable to the order of the person whose name appears on such certificate or certificates as the owner thereof and each surrendered certificate shall be cancelled. In the event less than all of the shares represented by any such certificate are redeemed, a new certificate shall be issued representing the unredeemed shares. From and after the Redemption Date, unless there shall have been a default in payment of the Redemption Price, all rights of the holders of shares of Series A Preferred designated for redemption in the Redemption Notice as holders of Series A Preferred (except the right to receive the Redemption Price without interest upon surrender of their certificate or certificates and except as provided in Section 6(c)) shall cease with respect to such shares, and such shares shall not thereafter be transferred on the books of the Company or be deemed to be outstanding for any purpose whatsoever.

SECTION 6. EXCHANGE RIGHT.

(a) At any time beginning on the date hereof and ending on June 30, 2002, provided that no shares of Series A Preferred representing the shares initially issued and sold by the Company to Elan International Services, Ltd., a Bermuda corporation ("EIS") and its affiliates, together with those issued or issuable in respect of dividends provided for in Section 1 above, have been converted as provided in Section 4(a) or (b)(ii) above, the holders of the Series A Preferred (by act of the holders of a majority of the Series A Preferred) shall have the right to exchange their shares of Series A Preferred (the "Exchange Right") with the Company for common shares of Orasense Ltd., a Bermuda corporation ("Newco"), held by the Company, representing 30.1% of the aggregate issued and outstanding capital stock of Newco, so that, after giving effect to the exercise of the Exchange Right, such holders will own 50.0% of such issued and outstanding capital stock of Newco.

(b) In order to exercise the Exchange Right, the holders shall provide written notice thereof to the Company, setting forth (i) the fact that such holders intend to exercise the

Exchange Right, and (ii) the proposed date for such exercise (the "Exercise Date"), which shall be between 10 and 30 days after the date of such notice. Such notice shall be irrevocable. On the Exercise Date, (y) the holders shall tender their shares of Series A Preferred to the Company for cancellation, and (z) the Company shall cause to be delivered to EIS, acting on behalf of such holders, such shares of Newco. The holders and the Company shall take all other necessary or appropriate actions in connection with or to effect such closing.

(c) If any shares of Series A Preferred are converted into shares of Common Stock pursuant to Section 4(a) or (b)(ii), the Exchange Right shall be terminated and be of no further force and effect with respect to such shares or with respect to those shares of Series A Preferred issued as dividends pursuant to Section 2(b). If all or any shares of the Series A Preferred are converted to shares of Common Stock upon the occurrence of a Significant Transaction, the Exchange Right shall be preserved for its full term as provided in Section 6(a), except that, to exercise the Exchange Right, EIS shall be obligated to tender the consideration received by EIS upon the automatic conversion of the Series A Preferred in connection with such Significant Transaction. If the Company exercises the Redemption Right with respect to any shares of Series A Preferred, the Exchange Right shall be preserved for its full six-year term, except that, to exercise the Exchange Right, EIS shall be obligated to tender the consideration received by EIS upon the redemption of any Excess Shares in connection with the Company's exercise of its Redemption Right.

SECTION 7. VOTING RIGHTS. Holders of Series A Preferred shall not be entitled to vote together with holders of Common Stock, including with respect to the election of directors of the Company, or as a separate class, except as otherwise provided by the General Corporation Law of the State of Delaware ("DGCL") and in this Section 8. To the extent that, under the DGCL, the vote of the holders of the Series A Preferred, voting separately as a class or series as applicable, is required to authorize a given action of the Company, the affirmative vote or consent of the holders of at least a majority of the shares of the Series A Preferred represented at a duly held meeting at which a quorum is present or by written consent of a majority of the shares of Series A Preferred (except as otherwise may be required under the DGCL) shall constitute the approval of such action by the class. Holders of the Series A Preferred shall be entitled to notice of all shareholder meetings or written consents (and copies of proxy materials and other information sent to shareholders) with respect to which they would be entitled as of right under the DGCL which notice would be provided pursuant to the Company's Bylaws and the DGCL.

SECTION 8. PROTECTIVE PROVISIONS. So long as any shares of Series A Preferred are outstanding, the Company shall not, without first obtaining the approval (by vote or written consent, as provided by law) of the holders of at least a majority of the then outstanding shares of Series A Preferred, voting as a separate class, amend its Certificate of Incorporation so as to adversely affect the rights, preferences or privileges of the Series A Preferred or any holder thereof, including, without limitation, by creating any series of Preferred Stock (or issuing shares under any such series) that is senior in right payment upon liquidation, in respect of dividends or otherwise to the Series A Preferred, or change the rights of the holders of the Series A Preferred in any other respect; provided, however, that the creation of any series of Preferred Stock (or issuance of shares under any such series) that is pari passu in right payment upon liquidation, in respect of dividends or otherwise with the Series A Preferred shall not be deemed to adversely

affect the rights, preferences or privileges of the Series A Preferred or any holder thereof or change the rights of the holders of the Series A Preferred in any other respect.

SECTION 9. STATUS OF CONVERTED, REDEEMED OR EXCHANGED STOCK. In the event any shares of Series A Preferred shall be converted pursuant to Section 4 hereof, redeemed pursuant to Section 5 hereof or exchanged pursuant to Section 6 hereof, the shares so converted, redeemed or exchanged shall be cancelled and shall not be reissuable by the Company.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Designation to be signed by its Chief Executive Officer and attested by its Secretary this 19th day of April, 1999.

ISIS PHARMACEUTICALS, INC.

By:

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Attest:

- ---
B. Lynne Parshall
Secretary

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" and to the use of our report dated January 30, 1999, in Amendment No. 3 to the Registration Statement (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.

/s/ ERNST & YOUNG LLP

ERNST & YOUNG LLP

San Diego, California
May 10, 1999

EXHIBIT 99.1

ISIS PHARMACEUTICALS, INC.

EMPLOYEE CONFIDENTIAL INFORMATION AND INVENTIONS AGREEMENT

In consideration of my employment or continued employment by Isis Pharmaceuticals, Inc., (the "Company"), and the compensation now and hereafter paid to me, I hereby agree as follows:

1. RECOGNITION OF COMPANY'S RIGHTS; NONDISCLOSURE. At all times during the term of my employment and thereafter, I will hold in strictest confidence and will not disclose, use, lecture upon or publish any of the Company's Confidential Information (defined below), except as such disclosure, use or publication may be required by the Company in connection with my work for the Company, or unless an officer of the Company expressly authorizes such in writing. I will not make any permitted disclosure, use or publication unless such disclosure, use or publication is in strict compliance with the Company's publication and presentation clearance policy. I will not export, directly or indirectly, any Company products, any direct product thereof, or any related technical data in violation of the United States Department of Commerce's Export Administration Regulations.

The term "Confidential Information" will mean trade secrets, confidential knowledge, data or any other proprietary information of the Company. By way of illustration but not limitation, "Confidential Information" includes (a) inventions, mask works, trade secrets, ideas, processes, formulas, source and object codes, data, programs, other works of authorship, know-how, improvements, discoveries, developments, designs and techniques (hereinafter collectively referred to as "Inventions"); and (b) information regarding plans for research, development, new products, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, suppliers and customers; as well as information regarding the skills and compensation of other employees of the Company.

2. THIRD PARTY INFORMATION. I understand, in addition, that the Company has received and in the future will receive from third parties confidential or proprietary information ("Third Party Information") subject to a duty on the Company's part to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of my employment and thereafter, I will hold Third Party Information in the strictest confidence and will not disclose (except as required to be disclosed in connection with my work for the Company) Third Party Information unless expressly authorized by an officer of the Company in writing. I will not make any permitted disclosures unless such disclosure is in strict compliance with the Company's publication and presentation clearance policy.

3. ASSIGNMENT OF INVENTIONS

3.1 ASSIGNMENT

(a) I hereby assign to the Company all my right, title and interest throughout the world in and to any and all Inventions (and all patent rights, copyrights, and all other rights in connection therewith, hereinafter referred to as "Proprietary Rights") whether or not patentable or registrable under patent, copyright, trademark or similar statutes (together with the goodwill associated therewith), made or conceived or reduced to practice or learned by me, either alone or jointly with others, during the period of my employment with the Company or within 1 year after termination of my employment, which relate to any Company Invention or to any work performed by me while I was employed by the Company. Inventions assigned to the Company by this Paragraph 3 are hereinafter referred to as "Company Inventions." I agree, upon request, to execute, verify and deliver assignments of such Proprietary Rights to the Company or its designee.

(b) If I am employed by the Company in the State of California, I recognize that this Agreement does not require assignment of any invention which qualifies fully for protection under Section 2870 of the California Labor Code (hereinafter "Section 2870"), which provides as follows:

(i) Any provision in an employment agreement which provides that an employee will assign, or offer to assign, any of his or her rights in an invention to his or her employer will not apply to an invention that the employee developed entirely on his or her own time without using the employer's equipment, supplies, facilities, or trade secret information except for those inventions that either:

(1) Relate at the time of conception or reduction to practice of the invention to the employer's business, or actual or demonstrably anticipated research or development of the employer.

(2) Result from any work performed by the employee for the employer.

(ii) To the extent a provision in an employment agreement purports to require an employee to assign an invention otherwise excluded from being required to be assigned under subdivision (i), the provision is against the public policy of this state and is unenforceable.

3.2 GOVERNMENT. I also agree to assign all my right, title and interest in and to any and all Company Inventions to the United States of America, if such is required to be assigned by a contract between the Company and United States of America or any of its agencies.

3.3 WORKS FOR HIRE. I acknowledge that all original works of authorship which are made by me (solely or jointly with others) within the scope of my employment as well as those works made by me within 1 year after termination of my employment which relate to any work made by me while I was employed by the Company and which are protectable by copyright are "works made for hire," as that term is defined in the United States Copyright Act (17 U.S.C., Section 101).

4. ENFORCEMENT OF PROPRIETARY RIGHTS. I will assist the Company in every proper way to obtain and from time to time enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. My obligation to assist the Company with respect to Proprietary Rights relating to such Company Inventions in any and all countries will continue beyond the termination of my employment, but the Company will compensate me at a reasonable rate after my termination for the time actually spent by me if the Company requests such assistance.

I hereby waive and transfer to the Company, any and all claims, of any nature whatsoever, which I now or may hereafter have, for infringement of any Proprietary Rights assigned hereunder to the Company.

5. OBLIGATION TO KEEP COMPANY INFORMED. During the period of my employment, I will promptly disclose all Company Inventions to the Company fully and in writing and will hold such Company Inventions in trust for the sole right and benefit of the Company. In addition, after termination of my employment, I will disclose all patent applications filed by me within a year after termination of employment which relate to any Company Invention or to any work performed by me while I was employed by Company.

6. PRIOR INVENTIONS. Inventions, if any, patented or unpatented, which I made prior to the commencement of my employment with the Company are excluded from the scope of this Agreement. To preclude any possible uncertainty, I have set forth in Exhibit A attached hereto a complete list of all Inventions that I have, alone or jointly with others, conceived, developed or reduced to practice or caused to be conceived, developed or reduced to practice prior to the commencement of my employment with the Company, that I consider to be my property or the property of third parties and that I wish to have excluded from the scope of this Agreement. If disclosure of any such Invention on Exhibit A would cause me to violate any prior confidentiality agreement, I understand that I am not to list such Inventions in Exhibit A but am to inform the Company that all such Inventions have not been listed for that reason.

7. ADDITIONAL ACTIVITIES.

(a) I agree that during the period of my employment by the Company I will not, without the Company's express written consent, engage in any employment or business

activity other than for the Company. Additionally, during the period of my employment by the Company and for 1 year after the date of termination of my employment with the Company I will not induce any employee of the Company to leave the employ of the Company.

(b) I acknowledge that the Company has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of the Company ("Trade Secret Information"). I further acknowledge that my use of such Trade Secret Information after the termination of my employment would cause the Company irreparable harm. Therefore, I agree that I will not use Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of the Company.

8. NO IMPROPER USE OF MATERIALS. During my employment by the Company I will not improperly use or disclose any confidential information or trade secrets, if any, of any former employer or any other person to whom I have an obligation of confidentiality, and I will not bring onto the premises of the Company any unpublished documents or any property belonging to any former employer or any other person to whom I have an obligation of confidentiality unless consented to in writing by that former employer or person.

9. NO CONFLICTING OBLIGATION. I represent that my performance (a) of all the terms of this Agreement and (b) as an employee of the Company, does not and will not breach any agreement to keep in confidence information acquired by me in confidence or in trust prior to my employment by the Company. I have not entered into, and I will not enter into, any agreement that conflicts with this Agreement.

10. RETURN OF COMPANY DOCUMENTS. When I leave the employ of the Company, I will deliver to the Company any and all laboratory notebooks, conception notebooks, drawings, notes, memoranda, specifications, devices, formulas, molecules, cells, storage media, including software and documents, including any computer printouts, together with all copies thereof, and any other material containing or disclosing any Company Inventions, Third Party Information or Confidential Information of the Company. I further agree that any property situated on the Company's premises and owned by the Company including disks and other storage media, filing cabinets or other work areas, is subject to inspection by Company personnel at any time with or without notice. Prior to leaving, I will cooperate with the Company in completing and signing the Company's termination statement for technical and management personnel.

11. LEGAL AND EQUITABLE REMEDIES. Because my services are personal and unique and because I may have access to and become acquainted with the Confidential Information of the Company, the Company will have the right to enforce this

Agreement and any of its provisions by injunction, specific performance or other equitable relief, without bond, without prejudice to any other rights and remedies that the Company may have for a breach of this Agreement.

12. NOTICES. Any notices required or permitted hereunder will be given to me at the address specified below or at such other address as I will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified and with confirmation copy following by another permitted method), telexed, sent by express courier service, or, if sent by certified or registered mail, three days after the date of mailing.

13. GENERAL PROVISIONS

13.1 GOVERNING LAW. This Agreement will be governed by and construed according to the laws of the State of California.

13.2 ENTIRE AGREEMENT. This Agreement is the final, complete and exclusive agreement of the parties with respect to the subject matter hereof and supersedes and merges all prior discussions between us. No modification or amendment to this Agreement, nor any waiver of any rights under this Agreement, will be effective unless in writing signed by both parties. Any subsequent change or changes in my duties, salary or compensation will not affect the validity or scope of this Agreement. As used in this Agreement, the period of my employment includes any time during which I may be retained by the Company as a consultant.

13.3 SEVERABILITY. If any of the provisions in this Agreement are deemed unenforceable by law, then the remaining provisions will continue in full force and effect.

13.4 SUCCESSORS AND ASSIGNS. This Agreement will be binding upon my heirs, executors, administrators and other legal representatives and will be for the benefit of the Company, its successors, and its assigns.

13.5 SURVIVAL. The provisions of this Agreement will survive the termination of my employment and the assignment of this Agreement by the Company to any successor in interest or other assignee.

13.6 EMPLOYMENT. I agree and understand that nothing in this Agreement will confer any right with respect to continuation of employment by the Company, nor will it interfere in any way with my right or the Company's right to terminate my employment at any time, with or without cause.

13.7 WAIVER. No waiver by the Company of any breach of this Agreement will be a waiver of any preceding or succeeding breach. No waiver by the Company of any right under this Agreement will be construed as a waiver of any other right. The Company will not be required to give notice to enforce strict adherence to all terms of this Agreement.

This Agreement will be effective as of the first day of my employment with the Company, namely: _____, 19____.

I UNDERSTAND THAT THIS AGREEMENT AFFECTS MY RIGHTS TO INVENTIONS I MAKE DURING MY EMPLOYMENT, AND RESTRICTS MY RIGHT TO DISCLOSE OR USE THE COMPANY'S CONFIDENTIAL INFORMATION DURING OR SUBSEQUENT TO MY EMPLOYMENT.

I HAVE READ THIS AGREEMENT CAREFULLY AND UNDERSTAND ITS TERMS. I HAVE COMPLETELY FILLED OUT EXHIBIT A TO THIS AGREEMENT.

Dated: ---------- ---------

Signature

Name of Employee

Address

ACCEPTED AND AGREED TO:

Isis Pharmaceuticals, Inc.

By:

Signature

Printed Name

Title

EXHIBIT A

ISIS PHARMACEUTICALS, INC.
2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008

1. The following is a complete list of all inventions or improvements relevant to the subject matter of my employment by Isis Pharmaceuticals, Inc. (the "Company") that have been made or conceived or first reduced to practice by me alone or jointly with others prior to my engagement by the Company:

[ ] No inventions or improvements. [ ] See below:

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[ ] Due to confidentiality agreements with prior employer, I cannot disclose certain inventions that would otherwise be included on the above-described list.

[ ] Additional sheets attached.

2. I propose to bring to my employment the following devices, materials and documents of a former employer or other person to whom I have an obligation of confidentiality that are not generally available to the public, which materials and documents may be used in my employment pursuant to the express written authorization of my former employer or such other person (a copy of which is attached hereto):

[ ] No material [ ] See below:

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[ ] Additional sheets attached.

Dated:
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Employee