AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON MARCH 31, 1999

REGISTRATION NO. 333-71911

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

AMENDMENT NO. 2
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 MARCH 31, 1999

PROSPECTUS

4,000,000 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

Isis is selling 4,000,000 shares of common stock. Isis' common stock is traded on the Nasdaq National Market under the symbol "ISIP". On March 29, 1999, the last reported sale price for our common stock on the Nasdaq National Market was $10.5625 per share.

Isis plans to enter into a common stock purchase agreement with Ridgeway Investment Limited. Under the purchase agreement, Isis may issue and sell, from time to time, shares of its common stock for cash consideration up to an aggregate of $42 million.

For a period of 28 months following the effective date of the registration statement of which this prospectus forms a part, Isis may, from time to time and at its sole discretion, present Ridgeway with draw down requests to sell up to $3,000,000 worth of shares of its common stock. Upon each draw down request, Isis will set the minimum price at which Isis will sell its shares of common stock to Ridgeway. The price of those shares will equal to 94.5% of the average price of the common stock over a period specified in the purchase agreement. Isis may present Ridgeway with up to 24 draw down notices during the term of the purchase agreement.

Upon receipt of a draw down request, Ridgeway may exercise a call option to purchase up to an additional $3,000,000 worth of shares of common stock for a purchase price equal to 95.5% of the average price of the common stock over a period specified in the purchase agreement.

As of the date of this prospectus, we have not issued any shares of common stock under the purchase agreement.

INVESTING IN OUR COMMON STOCK INVOLVES CERTAIN RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 3.

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

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 the Company as Executive Vice President overseeing corporate development, business development, strategic planning and marketing, human resources and operations, and investor relations. B. Lynne Parshall, Executive Vice President and Chief Financial Officer assumed responsibility for the Company's manufacturing and regulatory affairs activities in addition to her previous responsibilities.

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

THE OFFERING

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

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

RISK FACTORS

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

UNCERTAINTY ASSOCIATED WITH OUR CLINICAL TRIALS

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.

To begin the process, preclinical studies are conducted, first in the research laboratory and then in animals, to identify potential safety problems. If the research and preclinical development support further development, we must then submit an Investigational New Drug application to the FDA to obtain authorization for human clinical testing. However, our IND application may not be granted by the FDA.

Clinical trials are typically conducted in three sequential phases, although the phases may overlap. In Phase I, which typically involves giving the drug to healthy human subjects before giving it to patients, the drug candidate is tested for safety and tolerance. Phase II typically involves studies in a somewhat larger population of diseased patients to identify possible negative effects and safety risks, to begin gathering preliminary efficacy data and to investigate possible dose sizes and schedules. Phase III trials further evaluate the drug's efficacy and further test for safety within an expanded patient population. Once the clinical trials are completed, data from preclinical testing and clinical trials are submitted to the FDA in a New Drug Application in order to obtain approval to sell the drug.

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

OUR DRUG CANDIDATES ARE SUBJECT TO GOVERNMENT REGULATION AND PRODUCT APPROVALS

Our drug candidates under development are subject to regulation by the federal government, including the FDA, and by state and local governments. If our products are marketed abroad, they will also need to comply with export requirements and regulation by foreign governments. The applicable regulatory approval process is lengthy and expensive and must be completed prior to the commercialization of a product. 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 such approvals, failure to receive such 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.

Product development and approval to meet FDA regulatory requirements takes a number of years, involves the expenditure of substantial resources and is uncertain. Many products that initially appear promising ultimately do not reach the market because they are not found to be safe or effective. In addition, the current regulatory framework could change and additional regulations may arise at any stage of product development that may affect approval, delay the submission or review of an application or require additional expenditures.

WE CANNOT GUARANTEE MARKET ACCEPTANCE OF OUR PRODUCTS

We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which has achieved limited market acceptance in a small commercial market with significant competition. We delivered our first commercial shipment of Vitravene in 1998, earning product revenue of $560,000. We cannot guarantee that any of our products in development, if approved for marketing, will achieve market acceptance. The degree of market acceptance depends upon a number of factors, including:

- the receipt and scope of regulatory approvals,

- the establishment and demonstration in the medical and patient advocacy community of the clinical efficacy and safety of our product candidates and their potential advantages over competitive products, and

- reimbursement policies of government and third-party payors.

In addition, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will accept and utilize any products that may be developed by us.

WE DEPEND ON OUR COLLABORATIVE PARTNERS

We currently have agreements with Novartis Pharma, Boehringer Ingelheim, CIBA Vision, Merck & Co., Zeneca Pharmaceuticals, Abbot Laboratories as collaborative partners. These collaborative partners have agreed to pay for a portion of our research and development expenses. We have entered into research, development or distribution agreements pursuant to which the collaborative partners provide money in exchange for research services, product rights or marketing rights related to the products or targets involved. In addition, all of these agreements provide for us to receive royalties or other revenues based on sales of products developed or marketed by these collaborative partners.

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.

WE ARE IN THE EARLY STAGE OF DEVELOPMENT AND OUR PRODUCTS ARE SUBJECT TO TECHNOLOGICAL UNCERTAINTY

We are still at an early stage of development. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development 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. Drug discovery and development involves inherent risks including the risk that genetic targets that are identified prove unsuccessful and the risk that compounds that demonstrate attractive development characteristics in preclinical studies have undesirable side-effects, including toxicity. Laboratory results obtained in preclinical studies do not necessarily indicate the results that will be obtained in later stages of preclinical development or in human clinical testing. For example, we are attempting to develop products for diseases for which no appropriate animal model that might predict efficacy currently exists. As a result, drug candidates for these diseases must advance at least to Phase II human clinical trials before we will have evidence of efficacy outside of the laboratory. Drugs discovered by us may not effectively combat the targeted disease and, even if they work, may not be commercially successful.

WE HAVE A HISTORY OF OPERATING LOSSES

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.

WE MAY REQUIRE ADDITIONAL CAPITAL IN THE FUTURE

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. 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.

Our need for additional funding will also depend upon the cost of manufacturing products on a larger scale and our ability to establish and maintain effective marketing and sales activities and arrangements. If we find that we do not have enough money, additional funds may be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

WE HAVE LIMITED LARGE-SCALE MANUFACTURING EXPERIENCE

Our ability to operate profitably will depend in part on our ability to manufacture our drug products, or to have another company manufacture our products, at a cost low enough to enable us to charge a competitive price to buyers. To 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 be able to meet our supply needs for clinical trials.

NEW DRUG CANDIDATES AND COMPETITION MAY HURT OUR BUSINESS

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 PATENTS AND PROPRIETARY RIGHTS COULD AFFECT OUR ABILITY TO COMPETE

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

Litigation regarding patents and other intellectual property rights is extensive in the biotechnology industry. We are aware that patents have been applied for and in some cases issued to others claiming technologies which are closely related to ours. As a result, and in part due to the ambiguities and evolving nature of intellectual property law, we periodically receive notices from others that they are seeking patent rights that could, if obtained, negatively impact our business. However, to date, none of these notices has resulted in a negative impact on our business.

In the event of an intellectual property dispute, we may be forced to litigate. Such litigation could involve proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission, as well as affected third parties. 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.

WE HAVE NO EXPERIENCE IN SALES AND MARKETING

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

successful. As with any new product, our products may not achieve market acceptance in place of existing treatments.

WE DEPEND ON OUR KEY EMPLOYEES

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 IS 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.

ANTI-TAKEOVER PROVISIONS

Our certificate of incorporation provides for classified terms for the members of the board of directors. Our certificate also includes a provision 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, 1997;

- Quarterly Reports on Form 10-Q for the quarters ended March 31, 1998, June 30, 1998 and September 30, 1998;

- Proxy Statement for the 1998 Annual Meeting of Stockholders; 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 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. No such transactions are being planned or negotiated 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 $12.75 per share and the application of the estimated net proceeds therefrom (after deducting estimated offering expenses) the pro forma net tangible book value of Isis as of December 31, 1998 would have been $36,604,000 or $1.18 per share, an immediate increase in net tangible book value of $1.71 per share to existing stockholders and an immediate dilution in net tangible book value of $11.57 per share to purchasers of common stock in the offering, as illustrated in the following table:

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

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

SELECTED FINANCIAL DATA

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

	YEARS ENDED DECEMBER 31,		
	1998	1997	1996
	(IN THOUSANDS, EXCEPT PER SHARE AMOUNTS)		
STATEMENT OF OPERATIONS DATA:			
Revenues:			
Research and development revenues	$ 38,611	$ 32,722	$ 22,663
Product revenues	560	--	--
	39,171	32,722	22,663
Expenses:			
Research and development	62,200	55,940	45,653
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, 1997, and in our most recent quarterly report on Form 10-Q, which are on file with the U.S. Securities and Exchange Commission, a copy of which is available from the Company.

Since 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. which was written off in accordance with our accounting policies. 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 the Company's net operating loss and tax credit carryforwards. However, there may or may not be additional limitations arising from any future changes in ownership that may have a material adverse impact on 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. 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 the Company's $25 million private debt financing in October 1997 and bears the same terms and conditions. In conjunction with this follow-on transaction, 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.

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PLAN OF DISTRIBUTION

We plan to enter into a common stock purchase agreement with Ridgeway. Ridgeway and its pledgees, donees, transferees and other subsequent owners, may offer their shares at various times in one or more of the following transactions:

- in the over-the-counter market; or

- in privately negotiated transactions

at prevailing market prices at the time of sale, at prices related to those prevailing market prices, at negotiated prices or at fixed prices.

Ridgeway may also sell its shares under Rule 144 instead of under this prospectus, if Rule 144 is available for those sales.

The transactions in the shares may be effected by one or more of the following methods:

- ordinary brokerage transactions and transactions in which the broker solicits purchasers;

- purchases by a broker or dealer as principal, and the resale by that broker or dealer for its account under this prospectus, including resale to another broker or dealer;

- block trades in which the broker or dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal in order to facilitate the transaction; or

- negotiated transactions between selling stockholders and purchasers without a broker or dealer.

Ridgeway is an "underwriter" within the meaning of the Securities Act in connection with its sale of the shares purchased under the purchase agreement with Isis. Broker-dealers or other persons acting on the behalf of parties that participate in the distribution of the shares may also be deemed to be underwriters. Any commissions or profits they receive on the resale of the shares may be deemed to be underwriting discounts and commissions under the Securities Act.

During the time Ridgeway is engaged in distributing shares covered by this prospectus, Ridgeway will comply with the requirements of the Securities Act and Rule 10b-5 and Regulation M under the Exchange Act. Under those rules and regulations, they:

- may not engage in any stabilization activity in connection with our securities;

- must furnish each broker which offers shares of common stock covered by

this prospectus with the number of copies of this prospectus which are required by each broker; and

- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities other than as permitted under the Exchange Act.

In the purchase agreement with Ridgeway, we will agree to indemnify and hold harmless Ridgeway and each person who controls Ridgeway against certain liabilities, including liabilities under the Securities Act, which may be based upon, among other things, any untrue statement or alleged untrue statement of a material fact or any omission

or alleged omission of a material fact, unless made or omitted in reliance upon written information provided to us by Ridgeway.

We have agreed to bear the expenses incident to the registration of the shares, other than selling discounts and commissions. These expenses are estimated to be $100,000.

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, 1997, 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 the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

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

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

ERNST & YOUNG LLP

San Diego, California

January 30, 1999

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

	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 generally 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 fourth quarter of 1998 and recorded $560,000 in net product revenues. For the years ended December 31, 1998 and December 31, 1997, Isis also earned contract revenue of $7,500,000 and $5,000,000, respectively, under the CIBA Vision agreement.

In July 1995, 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. 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.

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.

4,000,000 SHARES

ISIS PHARMACEUTICALS, INC.

COMMON STOCK

TABLE OF CONTENTS

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all expenses payable by 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)
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 Common Stock Purchase Agreement to be entered into between Isis and Ridgeway Investment Limited.

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

ITEM 17. UNDERTAKINGS

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

The undersigned registrant hereby undertakes:

(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. 2 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 31st day of March, 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. 2 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)	March 31, 1999
* B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	March 31, 1999

SIGNATURES	TITLE	DATE
*	Director	March 31, 1999
Alan C. Mendelson		
*	Director	March 31, 1999
Christopher F.O. Gabrieli		
*	Director	March 31, 1999
William R. Miller		
*	Director	March 31, 1999
Mark B. Skaletsky		
*	Director	March 31, 1999
Larry Soll, Ph.D.		
*	Director	March 31, 1999
Joseph H. Wender		
	Director	March 31, 1999
Burkhard Blank		

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

EXHIBIT INDEX

EXHIBIT NO.	DESCRIPTION	SEQUENTIAL PAGE NO.
4.1	Amended and Restated Certificate of Incorporation(1).....	
4.2	By-laws(1).....	
5.1	Opinion of Grantland E. Bryce.....	
23.1	Consent of Ernst & Young LLP.....	
23.2	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.....	
24.1	Power of Attorney. Reference is made to page II-5.....	
27.1	Financial Data Schedule.....	
99.1	Form of Common Stock Purchase Agreement to be entered into between Isis and Ridgeway Investment Limited.	

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

EXHIBIT 5.1

OPINION OF GRANTLAND E. BRYCE

March 30, 1999

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

Ladies and Gentlemen:

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

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

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

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

Very truly yours,

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

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Amendment No. 2 to Form S-3 No. 333-71911), and related Prospectus of Isis Pharmaceuticals, Inc for the registration of 4,000,000 shares of its common stock to be filed with the Securities and Exchange Commission on March 31, 1999, and to the incorporation by reference therein of our report dated January 23, 1998, with respect to the financial statements and schedule of Isis Pharmaceuticals, Inc. included in its Annual Report on Form 10-K for the year ended December 31, 1997, filed with the Securities and Exchange Commission. We also consent to the use of our report dated January 30, 1999 with respect to the financial statements of Isis Pharmaceuticals, Inc. for the year ended December 31, 1998 in the above mentioned registration statement and prospectus.

ERNST & YOUNG LLP

San Diego, California
March 30, 1999

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

1,000

YEAR
DEC-31-1998
JAN-01-1998
DEC-31-1998
27,618
31,230
3,466
0
0
63,187
21,542
0
96,074
22,536
77,724
0
0
27
(4,213)
96,074
560
43,321
0
0
76,949
0
9,355
(42,983)
0
(42,983)
0
0
0
(42,983)
(1.60)
(1.60)

EXHIBIT 99.1

COMMON STOCK PURCHASE AGREEMENT

DATED AS OF _____, 1999

BY AND BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

RIDGEWAY INVESTMENT LIMITED

TABLE OF CONTENTS

COMMON STOCK PURCHASE AGREEMENT

This COMMON STOCK PURCHASE AGREEMENT (this "Agreement") is dated as of _____, 1999 by and among between Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company") and Ridgeway Investment Limited, a corporation incorporated in the Commonwealth of The Bahamas as an International Business Company (the "Purchaser").

The parties hereto agree as follows:

ARTICLE I

DEFINITIONS

Section I.1 Definitions.

(a) "Call Option" shall have the meaning assigned to such term in Section 6.2 hereof.

(b) "Call Option Notice" shall mean a notice sent to the Company on the trading day the Purchaser elects to exercise a Call Option.

(c) "Commission Documents" shall have the meaning assigned to such term in Section 3.1(f) hereof.

(d) "Commission Filings" means the Company's Form 10-K for the fiscal year ended December 31, 1998, Registration Statement on Form S-3 No. 333-71911, and all other filings made by the Company after the date hereof pursuant to the Securities Exchange Act of 1934.

(e) "Draw Down Amount" means the actual amount of a Draw Down up to $3,000,000.

(f) "Draw Down Notice" shall have the meaning assigned to such term in Section 6.1(k) hereof.

(g) "Draw Down Pricing Period" shall mean a period of eighteen (18) consecutive trading days following a Draw Down Notice.

(h) "Effective Date" shall mean the date the Registration Statement of the Company covering the Shares being subscribed for hereby is declared effective.

(i) "Material Adverse Effect" shall mean any effect on the business, operations, properties or financial condition of the Company that is material and adverse to the Company and its subsidiaries, taken as a whole and/or any condition, circumstance, or situation that would prohibit the Company from entering into and performing any of its obligations under this Agreement in any material respect.

(j) "Material Change in Ownership" shall mean that the officers and directors of the Company shall beneficially own in the aggregate less than 2% of the outstanding Common Stock of the Company that the officers and directors beneficially own as of the date hereof.

(k) "Prospectus" as used in this Agreement means the prospectus in the form included in the Registration Statement, or, if the prospectus included in the Registration Statement omits information in reliance on Rule 430A under the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder (collectively, the "Securities Act"), and such information is included in a prospectus filed with the Commission pursuant to Rule 424(b) under the Securities Act, the term "Prospectus" as used in this Agreement means the prospectus in the form included in the Registration Statement as supplemented by the addition of the Rule 430A information contained in the prospectus filed with the Commission pursuant to Rule 424(b).

(l) "Registration Statement" shall mean the registration statement on Form S-3, Commission File Number 333-71911 under the Securities Act, filed with the Securities and Exchange Commission for the registration of the Shares, as such Registration Statement may be amended from time to time.

(m) "Settlement Date" shall have the meaning assigned to such term in Section 6.1(b) hereof.

(n) "Shares" shall mean, collectively, the shares of Common Stock of the Company being subscribed for hereunder and those shares of Common Stock issuable to the Purchaser upon exercise of the Call Option.

(o) "Threshold Price" is the lowest VWAP at which the Company will sell Shares during each Draw Down Pricing Period.

(p) "Total Value" shall mean the product of the VWAP and the total volume of the shares of Common Stock traded on NASDAQ on the day the Call Option Notice is issued as reported by Bloomberg Financial LP using the AQR function.

(q) "VWAP" shall mean the daily volume weighted average price (based on a trading day from 9:30 a.m. to 4:00 p.m.) of the Company on NASDAQ (or any successor thereto) as reported by Bloomberg Financial LP using the AQR function.

ARTICLE II

PURCHASE AND SALE OF COMMON STOCK

Section II.1 Purchase and Sale of Stock. Subject to the terms and conditions of this Agreement, the Company shall issue and sell to the Purchaser and the Purchaser shall purchase from the Company up to $144,000,000 of the Company's common stock, $.001 par value per share (the "Common Stock"), based on up to twenty-four (24) Draw Downs of up to $3,000,000 per Draw Down, and Call Options which may be exercised during any Draw Down Pricing Period of up to $3,000,000 per Call Option. In no event shall the amount of Common Stock purchased by the Purchaser exceed $3,000,000 per Draw Down or $3,000,000 per Call Option.

Section II.2 The Shares. The Company has authorized and has reserved and covenants to continue to reserve, subject to Section 4.5(b) hereof, free of preemptive rights and other similar contractual rights of stockholders, a sufficient number of its authorized but unissued shares of its Common Stock to cover the Shares to be issued in connection with all Draw Downs and Call Options requested under this Agreement.

Section II.3 Registration Statement and Prospectus. The Company has prepared and filed with the Securities and Exchange Commission (the "Commission") in accordance with the provisions of the Securities Act, the Registration Statement, including a prospectus subject to completion relating to the Shares.

Section II.4 Purchase Price and Closing. The Company agrees to issue and sell to the Purchaser and, in consideration of and in express reliance upon the representations, warranties, covenants, terms and conditions of this Agreement, the Purchaser, agrees to purchase that number of the Shares to be issued in connection with each Draw Down and exercise of each Call Option. The closing under this Agreement shall take place at the offices of Parker Chapin Flattau & Klimpl, LLP 1211 Avenue of the Americas, New York, NY 10036 (the "Closing") at 10:00 a.m. E.S.T. on (i) March __, 1999, or (ii) such other time and place or on such date as the Purchaser and the Company may agree upon (the "Closing Date"). Each party shall deliver all documents, instruments and writings required to be delivered by such party pursuant to this Agreement at or prior to the Closing.

ARTICLE III

REPRESENTATIONS AND WARRANTIES

Section III.1 Representation and Warranties of the Company. The Company hereby makes the following representations and warranties to the Purchaser:

(a) Organization, Good Standing and Power. The Company is a corporation duly incorporated, validly existing and in good standing under the laws of Delaware and has the requisite corporate power to own, lease and operate its properties and assets and to conduct its business as it is now being conducted. As of the date hereof, the Company does not have any subsidiaries (as defined in Section 3.1(g)) except as set forth in the Registration Statement and in the Company's most recent Form 10-K, including the accompanying financial statements (the "Form 10-K"), or in the Company's most recent Form 10-Q (the "Form 10-Q"), or on Schedule 3.1(a) attached hereto. The Company and each such subsidiary is duly qualified as a foreign corporation to do business and is in good standing in every jurisdiction in which the nature of the business conducted or property owned by it makes such qualification necessary except for any jurisdiction in which the failure to be so qualified will not have a material adverse effect on the Company's financial condition.

(b) Authorization; Enforcement. The Company has the requisite corporate power and authority to enter into and perform this Agreement and to issue and sell the Shares in accordance with the terms hereof. The execution, delivery and performance of this Agreement by the Company and the consummation by it of the transactions contemplated hereby have been duly and validly authorized by all necessary corporate action, and, except as contemplated by Section 4.5(b), no further consent or authorization of the Company or its Board of Directors or stockholders is required. This Agreement has been duly executed and delivered by the Company. This Agreement constitutes, or shall constitute when executed and delivered, a valid and binding obligation of the Company enforceable against the Company in accordance with its terms, except as such enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium, liquidation, conservatorship, receivership or similar laws relating to, or affecting generally the enforcement of, creditor's rights and remedies or by other equitable principles of general application.

(c) Capitalization. The authorized capital stock of the Company and the shares thereof issued and outstanding as of the date hereof are set forth in the Registration Statement or on Schedule 3.1(c) attached hereto. All of the outstanding shares of the Company's Common Stock have been duly and validly authorized, and are fully paid and nonassessable. Except as set forth in this Agreement or as set forth in the Registration Statement, the Commission Documents or the Commission Filings or on Schedule 3.1(c) attached hereto, as of the date hereof, no shares of Common Stock are entitled to preemptive rights or registration rights and there are no outstanding options, warrants, scrip, rights to subscribe to, call or commitments of any character whatsoever relating to, or securities or rights convertible into, any shares of capital stock of the Company.

Furthermore, except as set forth in this Agreement, the Registration Statement, the Commission Documents or the Commission Filings or on Schedule 3.1(c) attached hereto, as of the date hereof, there are no contracts, commitments, understandings, or arrangements by which the Company is or may become bound to issue additional shares of the capital stock of the Company or options, securities or rights convertible into shares of capital stock of the Company. Except for customary transfer restrictions contained in agreements entered into by the Company in order to sell restricted securities or as described in the Registration Statement, the Commission Documents or the Commission Filings, or on Schedule 3.1(c) attached hereto, as of the date hereof, the Company is not a party to any agreement granting registration rights to any person with respect to any of its equity or debt securities. Except as set forth in the Registration Statement, the Commission Documents or the Commission Filings or on Schedule 3.1(c) attached hereto, as of the date hereof, the Company is not a party to, and it has no knowledge of, any agreement restricting the voting or transfer of any shares of the capital stock of the Company. Except as set forth in the Registration Statement, the Commission Documents or the Commission Filings or on Schedule 3.1(c) attached hereto, the offer and sale of all capital stock, convertible securities, rights, warrants, or options of the Company issued prior to the Closing complied with all applicable federal and state securities laws, and no stockholder has a right of rescission or damages with respect thereto which would have a Material Adverse Effect on the Company's financial condition or operating results. The Company has furnished or made available to the Purchaser true and correct copies of the Company's Certificate of Incorporation as in effect on the date hereof (the "Articles"), and the Company's Bylaws as in effect on the date hereof (the "Bylaws").

(d) Issuance of Shares. The Shares to be issued under this Agreement have been duly authorized by all necessary corporate action and, when paid for or issued in accordance with the terms hereof, the Shares shall be validly issued and outstanding, fully paid and nonassessable, and the Purchaser shall be entitled to all rights accorded to a holder of Common Stock.

(e) No Conflicts. Except as disclosed on Schedule 3.1(e) attached hereto, the execution, delivery and performance of this Agreement by the Company and the consummation by the Company of the transactions contemplated therein do not (i) violate any provision of the Company's Articles or Bylaws, (ii) conflict with, or constitute a default (or an event which with notice or lapse of time or both would become a default) under, or give to others any rights of termination, amendment, acceleration or cancellation of, any material agreement, mortgage, deed of trust, indenture, note, bond, license, lease agreement, instrument or obligation to which the Company is a party, (iii) create or impose a lien, charge or encumbrance on any property of the Company under any agreement or any commitment to which the Company is a party or by which the Company is bound or by which any of its respective properties or assets are bound, or (iv) result in a violation of any federal, state, local or foreign statute, rule, regulation, order, judgment or decree (including federal and state securities laws and regulations) applicable to the Company or any of its subsidiaries or by which any property or asset of the Company or any of its subsidiaries are bound or affected, except, in all cases, for such conflicts, defaults, terminations, amendments, acceleration, cancellations and violations as would not, individually or in the aggregate, have a Material Adverse Effect. The Company is not required under federal, state or local law, rule or

regulation to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency in order for it to execute, deliver or perform any of its obligations under this Agreement, or issue and sell the Shares in accordance with the terms hereof (other than any filings which may be required to be made by the Company with the Securities and Exchange Commission (the "Commission"), or Nasdaq subsequent to the Closing, and, any registration statement which may be filed pursuant hereto); provided that, for purpose of the representation made in this sentence, the Company is assuming and relying upon the accuracy of the relevant representations and agreements of the Purchaser herein.

(f) Commission Documents, Financial Statements. The Common Stock of the Company is registered pursuant to Section 12(b) or 12(g) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and, except as disclosed in the Registration Statement, or the Commission Documents or the Commission Filings or on Schedule 3.1(f) attached hereto, as of the date hereof, the Company has timely filed all reports, schedules, forms, statements and other documents required to be filed by it with the Commission pursuant to the reporting requirements of the Exchange Act, including material filed pursuant to Section 13(a) or 15(d) of the Exchange Act (all of the foregoing including filings incorporated by reference therein being referred to herein as the "Commission Documents"). The Company has delivered or made available to the Purchaser true and complete copies of the Commission Documents filed with the Commission since December 31, 1998 and prior to the Closing Date. The Company has not provided to the Purchaser any information which, according to applicable law, rule or regulation, should have been disclosed publicly by the Company but which has not been so disclosed, other than with respect to the transactions contemplated by this Agreement. As of their respective dates, the Form 10-K for the year ended December 31, 1998 complied in all material respects with the requirements of the Exchange Act and the rules and regulations of the Commission promulgated thereunder and other federal, state and local laws, rules and regulations applicable to such documents, and, as of their respective dates, such Form 10-K did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading. The financial statements of the Company included in the Commission Documents comply as to form in all material respects with applicable accounting requirements and the published rules and regulations of the Commission or other applicable rules and regulations with respect thereto. Such financial statements have been prepared in accordance with generally accepted accounting principles ("GAAP") applied on a consistent basis during the periods involved (except (i) as may be otherwise indicated in such financial statements or the notes thereto or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes or may be condensed or summary statements), and fairly present in all material respects the financial position of the Company and its subsidiaries as of the dates thereof and the results of operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal year-end audit adjustments).

(g) Subsidiaries. The Commission Documents or Schedule 3.1(g) attached hereto set forth each subsidiary of the Company as of the date hereof, showing the jurisdiction of its incorporation or organization and showing the percentage of each person's ownership of the outstanding stock or other interests of such subsidiary. For the purposes of this Agreement,

"subsidiary" shall mean any corporation or other entity of which at least a majority of the securities or other ownership interest having ordinary voting power (absolutely or contingently) for the election of directors or other persons performing similar functions are at the time owned directly or indirectly by the Company and/or any of its other subsidiaries. Except as set forth in the Commission Documents or the Commission Filings, none of such subsidiaries is a "significant subsidiary" as defined in Regulation S-X.

(h) No Material Adverse Change. Since December 31, 1998, the Company has not experienced or suffered any Material Adverse Effect.

(i) No Undisclosed Liabilities. Except as disclosed in the Commission Documents or the Commission Filings or on Schedule 3.1(i) attached hereto, neither the Company nor any of its subsidiaries has any liabilities, obligations, claims or losses (whether liquidated or unliquidated, secured or unsecured, absolute, accrued, contingent or otherwise) that would be required to be disclosed on a balance sheet of the Company or any subsidiary (including the notes thereto) in conformity with GAAP not disclosed in the Commission Documents, other than those incurred in the ordinary course of the Company's or its subsidiaries respective businesses since December 31, 1998 and which, individually or in the aggregate, do not or would not have a Material Adverse Effect on the Company or its subsidiaries.

(j) No Undisclosed Events or Circumstances. No event or circumstance has occurred or exists with respect to the Company or its subsidiaries or their respective businesses, properties, prospects, operations or financial condition, which, under applicable law, rule or regulation, requires public disclosure or announcement by the Company but which has not been so publicly announced or disclosed and which, individually or in the aggregate, do not or would not have a Material Adverse Effect on the Company or its subsidiaries.

(k) Indebtedness. The Form 10-K sets forth as of December 31, 1998 all outstanding secured and unsecured Indebtedness of the Company or any subsidiary, or for which the Company or any subsidiary has commitments. For the purposes of this Agreement, "Indebtedness" shall mean (a) any liabilities for borrowed money or amounts owed in excess of $100,000 (other than trade accounts payable incurred in the ordinary course of business), (b) all guaranties, endorsements and other contingent obligations in respect of Indebtedness of others, whether or not the same are or should be reflected in the Company's balance sheet (or the notes thereto), except guaranties by endorsement of negotiable instruments for deposit or collection or similar transactions in the ordinary course of business; and (c) the present value of any lease payments in excess of $100,000 due under leases required to be capitalized in accordance with GAAP. Neither the Company nor any subsidiary is in default with respect to any Indebtedness.

(l) Title to Assets. Each of the Company and the subsidiaries has good and marketable title to all of its real and personal property reflected in the Commission Documents, free of any mortgages, pledges, charges, liens, security interests or other encumbrances, except for those indicated in the Commission Documents or the Commission Filings or on Schedule 3.1(l) attached hereto or such that could not reasonably be expected to cause a Material Adverse Effect on the

Company's financial condition or operating results. All said leases of the Company and each of its subsidiaries are valid and subsisting and in full force and effect in all material respects.

(m) Actions Pending. There is no action, suit, claim, investigation or proceeding pending or, to the knowledge of the Company, threatened against the Company or any subsidiary which questions the validity of this Agreement or the transactions contemplated hereby or any action taken or to be taken pursuant hereto or thereto. Except as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(m) attached hereto, there is no action, suit, claim, investigation or proceeding pending or, to the knowledge of the Company, threatened, against or involving the Company, any subsidiary or any of their respective properties or assets and which, if adversely determined, is reasonably likely to result in a Material Adverse Effect.

(n) Compliance with Law. The business of the Company and the subsidiaries has been and is presently being conducted in accordance with all applicable federal, state and local governmental laws, rules, regulations and ordinances, except as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(n) attached hereto or such that do not cause a Material Adverse Effect. The Company and each of its subsidiaries have all franchises, permits, licenses, consents and other governmental or regulatory authorizations and approvals necessary for the conduct of its business as now being conducted by it unless the failure to possess such franchises, permits, licenses, consents and other governmental or regulatory authorizations and approvals, individually or in the aggregate, could not reasonably be expected to have a Material Adverse Effect.

(o) Certain Fees. Except as set forth on Schedule 3.1(o) attached hereto, no brokers, finders or financial advisory fees or commissions will be payable by the Company or any subsidiary with respect to the transactions contemplated by this Agreement.

(p) Disclosure. To the best of the Company's knowledge, neither this Agreement or the Schedules hereto nor any other documents, certificates or instruments furnished to the Purchaser by or on behalf of the Company or any subsidiary in connection with the transactions contemplated by this Agreement contain any untrue statement of a material fact or omits to state a material fact necessary in order to make the statements made herein or therein, in the light of the circumstances under which they were made herein or therein, not misleading.

(q) Operation of Business. The Company or one of the subsidiaries owns or possesses all patents, trademarks, service marks, trade names, copyrights, licenses and authorizations as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(q) attached hereto and all rights with respect to the foregoing, which are necessary for the conduct of its business as now conducted without any conflict with the rights of others, except to the extent set forth in the Commission Documents or that a Material Adverse Effect could not reasonably be expected to result from such conflict.

(r) Environmental Compliance. Except as disclosed in the Commission Filings or on Schedule 3.1(r) attached hereto, the Company and each of its subsidiaries have obtained all

material approvals, authorization, certificates, consents, licenses, orders and permits or other similar authorizations of all governmental authorities, or from any other person, that are required under any Environmental Laws. "Environmental Laws" shall mean all applicable laws relating to the protection of the environment including, without limitation, all requirements pertaining to reporting, licensing, permitting, controlling, investigating or remediating emissions, discharges, releases or threatened releases of hazardous substances, chemical substances, pollutants, contaminants or toxic substances, materials or wastes, whether solid, liquid or gaseous in nature, into the air, surface water, groundwater or land, or relating to the manufacture, processing, distribution, use, treatment, storage, disposal, transport or handling of hazardous substances, chemical substances, pollutants, contaminants or toxic substances, material or wastes, whether solid, liquid or gaseous in nature. Except for such instances as would not individually or in the aggregate have a Material Adverse Effect, to the best of the Company's knowledge, there are no past or present events, conditions, circumstances, incidents, actions or omissions relating to or in any way affecting the Company or its subsidiaries that violate or could reasonably be expected to violate any Environmental Law after the Closing or that could reasonably be expected to give rise to any environmental liability, or otherwise form the basis of any claim, action, demand, suit, proceeding, hearing, study or investigation (i) under any Environmental Law, or (ii) based on or related to the manufacture, processing, distribution, use, treatment, storage (including without limitation underground storage tanks), disposal, transport or handling, or the emission, discharge, release or threatened release of any hazardous substance.

(s) Material Agreements. Except as set forth in the Commission Documents or on Schedule 3.1(s) attached hereto, neither the Company nor any subsidiary is a party to any written or oral contract, instrument, agreement, commitment, obligation, plan or arrangement, a copy of which would be required to be filed with the Commission as an exhibit to a registration statement on Form S-3 or applicable form (collectively, "Material Agreements") if the Company or any subsidiary were registering securities under the Securities Act. The Company and each of its subsidiaries has in all material respects performed all the obligations required to be performed by them to date under the foregoing agreements, have received no notice of default and, to the best of the Company's knowledge are not in default under any Material Agreement now in effect, the result of which could reasonably be expected to cause a Material Adverse Effect.

(t) Transactions with Affiliates. Except as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(t) attached hereto, there are no loans, leases, agreements, contracts, royalty agreements, management contracts or arrangements or other continuing transactions exceeding $100,000 between (a) the Company, any subsidiary or any of their respective customers (excluding agreements related to the purchase or lease of the Company's products) or suppliers on the one hand, and (b) on the other hand, any officer, employee, consultant or director of the Company, or any of its subsidiaries, or any person who would be covered by Item 404(a) of Regulation S-K or any corporation or other entity controlled by such officer, employee, consultant, director or person.

(u) Securities Act of 1933. The Company has complied in all material respects with all applicable federal and state securities laws in connection with the offer, issuance and sale

of the Shares hereunder.

(i) Each Prospectus included as part of the Registration Statement as originally filed or as part of any amendment or supplement thereto, or filed pursuant to Rule 424 under the Securities Act, complied when so filed in all material respects with the provisions of the Securities Act. The Commission has not issued any order preventing or suspending the use of any Prospectus.

(ii) The Company meets the requirements for the use of Form S-3 under the Securities Act. The Registration Statement in the form in which it became effective and also in such form as it may be when any post-effective amendment thereto became effective and the Prospectus and any supplement or amendment thereto when filed with the Commission under Rule 424(b) under the Securities Act, complied in all material respects with the provisions of the Securities Act and did not at any such times contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein (in the case of the Prospectus, in the light of the circumstances under which they made) not misleading, except that this representation and warranty does not apply to statements in or omissions from the Registration Statement or the Prospectus made in reliance upon and in conformity with information relating to the Purchaser furnished to the Company in writing by or on behalf of the Purchaser through you expressly for use therein.

(iii) The Company has not distributed and, prior to the completion of the distribution of the Shares, will not distribute any offering material in connection with the offering and sale of the Shares other than the Registration Statement, the Prospectus or other materials, if any, permitted by the Securities Act.

(v) Employees. As of the date hereof, neither the Company nor any subsidiary has any collective bargaining arrangements or agreements covering any of its employees, except as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(v) attached hereto. As of the date hereof, except as set forth in the Commission Documents or the Commission Filings or on Schedule 3.1(v) attached hereto, neither the Company nor any subsidiary has any employment contract, agreement regarding proprietary information, noncompetition agreement, nonsolicitation agreement, confidentiality agreement, or any other similar contract or restrictive covenant, relating to the right of any officer, employee or consultant to be employed or engaged by the Company or such subsidiary. As of the date hereof, since December 31, 1998, except as disclosed in the Registration Statement, the Commission Documents or the Commission Filings or Schedule 3.1(v), no officer, consultant or key employee of the Company or any subsidiary whose termination, either individually or in the aggregate, could reasonably be expected to have a Material Adverse Effect, has terminated or, to the knowledge of the Company, has any present intention of terminating his or her employment or engagement with the Company or any subsidiary.

(w) Use of Proceeds. The proceeds from the sale of the Shares will be used by the Company and its subsidiaries for general corporate purposes.

(x) Public Utility Holding Company Act and Investment Company Act Status. The Company is not a "holding company" or a "public utility company" as such terms are defined in the Public Utility Holding Company Act of 1935, as amended. The Company is not, and as a result of and immediately upon Closing will not be, an "investment company" or a company "controlled" by an "investment company," within the meaning of the Investment Company Act of 1940, as amended.

(y) ERISA. No liability to the Pension Benefit Guaranty Corporation has been incurred with respect to any Plan by the Company or any of its subsidiaries which is or would have a Material Adverse Effect. The execution and delivery of this Agreement and the issue and sale of the Shares will not involve any transaction which is subject to the prohibitions of Section 406 of ERISA or in connection with which a tax could be imposed pursuant to Section 4975 of the Internal Revenue Code of 1986, as amended, provided that, if any of the Purchaser, or any person or entity that owns a beneficial interest in any of the Purchaser, is an "employee pension benefit plan" (within the meaning of Section 3(2) of ERISA) with respect to which the Company is a "party in interest" (within the meaning of Section 3(14) of ERISA), the requirements of Sections 407(d)(5) and 408(e) of ERISA, if applicable, are met. As used in this Section 2.1(ac), the term "Plan" shall mean an "employee pension benefit plan" (as defined in Section 3 of ERISA) which is or has been established or maintained, or to which contributions are or have been made, by the Company or any subsidiary or by any trade or business, whether or not incorporated, which, together with the Company or any subsidiary, is under common control, as described in Section 414(b) or (c) of the Code.

(z) Acknowledgment Regarding Purchaser's Purchase of Shares. The Company acknowledges and agrees that the Purchaser is acting solely in the capacity of arm's length purchaser with respect to this Agreement and the transactions contemplated hereunder. The Company further acknowledges that the Purchaser is not acting as a financial advisor or fiduciary of the Company (or in any similar capacity) with respect to this Agreement and the transactions contemplated hereunder and any advice given by the Purchaser or any of its representatives or agents in connection with this Agreement and the transactions contemplated hereunder is merely incidental to the Purchaser's purchase of the Shares.

Section III.2 Representations and Warranties of the Purchaser. The Purchaser hereby makes the following representations and warranties to the Company:

(a) Organization and Standing of the Purchaser. The Purchaser is a corporation duly incorporated, validly existing and in good standing under the laws of the Commonwealth of the Bahamas.

(b) Authorization and Power. The Purchaser has the requisite corporate power and authority to enter into and perform this Agreement and to purchase the Shares in accordance with the terms hereof. The execution, delivery and performance of this Agreement by Purchaser and the consummation by it of the transactions contemplated hereby have been duly authorized by

all necessary corporate action, and no further consent or authorization of the Purchaser, its Board of Directors or stockholders is required. This Agreement constitutes, or shall constitute when executed and delivered, a valid and binding obligation of the Purchaser enforceable against the Purchaser in accordance with its terms, except as such enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium, liquidation, conservatorship, receivership, or similar laws relating to, or affecting generally the enforcement of, creditor's rights and remedies or by other equitable principles of general application.

(c) No Conflicts. The execution, delivery and performance of this Agreement and the consummation by the Purchaser of the transactions contemplated hereby and thereby or relating hereto do not and will not (i) result in a violation of such Purchaser's charter documents or bylaws or (ii) conflict with, or constitute a default (or an event which with notice or lapse of time or both would become a default) under, or give to others any rights of termination, amendment, acceleration or cancellation of any material agreement, mortgage, deed of trust, indenture, note, bond, license, lease agreement, instrument or obligation to which the Purchaser is a party, (iii) create or impose or lien, charge or encumrance on any property of the Purchaser under any agreement or any commitment to which the Purchaser is party or by which the Purchaser is on or by which any of its respective properties or assets are bound or (iv) result in a violation of any law, rule, or regulation, or any order, judgment or decree of any court or governmental agency applicable to the Purchaser or its properties, except for such conflicts, defaults and violations as would not, individually or in the aggregate, prohibit or otherwise interfere with the ability of the Purchaser to enter into and perform its obligations under this Agreement in any material respect. The Purchaser is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency in order for it to execute, deliver or perform any of its obligations under this Agreement or to purchase the Shares in accordance with the terms hereof, provided that for purposes of the representation made in this sentence, the Purchaser is assuming and relying upon the accuracy of the relevant representations and agreements of the Company herein.

(d) Information. The Purchaser and its advisors, if any, have been furnished with all materials relating to the business, finances and operations of the Company and materials relating to the offer and sale of the Shares which have been requested by the Purchaser. The Purchaser and its advisors, if any, have been afforded the opportunity to ask questions of the Company. The Purchaser has sought such accounting, legal and tax advice as it has considered necessary to make an informed investment decision with respect to its acquisition of the Shares. Investor understands that it (and not the Company) shall be responsible for its own tax liabilities that may arise as a result of this investment or the transactions contemplated by this Agreement.

ARTICLE IV

COVENANTS

The Company covenants with the Purchaser as follows, which covenants are for the benefit of the Purchaser and its permitted assignees (as defined herein).

Section IV.1 Securities Compliance. The Company shall notify the Commission and NASD, if applicable, in accordance with their rules and regulations, of the transactions contemplated by this Agreement, and shall take all other necessary action and proceedings as may be required and permitted by applicable law, rule and regulation, for the legal and valid issuance of the Shares to the Purchaser or subsequent holders.

Section IV.2 Registration and Listing. The Company will take all action necessary to cause its Common Stock to continue to be registered under Sections 12(b) or 12(g) of the Exchange Act, will comply in all respects with its reporting and filing obligations under the Exchange Act, and will not take any action or file any document (whether or not permitted by the Securities Act or the rules promulgated thereunder) to terminate or suspend such registration or to terminate or suspend its reporting and filing obligations under the Exchange Act or Securities Act, except as permitted herein. The Company will take all action necessary to continue the listing or trading of its Common Stock and the listing of the Shares purchased by Purchaser hereunder on the NASDAQ or any relevant market or system, if applicable, and will comply in all respects with the Company's reporting, filing and other obligations under the bylaws or rules of the NASD or any relevant market or system.

Section IV.3 Registration Statement. Before the Purchaser shall be obligated to accept a Draw Down request from the Company, the Company shall have caused a sufficient number of shares of Common Stock to be registered to cover the Shares to be issued in connection with this Agreement.

Section IV.4 Distribution of Common Stock. The Company and the Purchaser agree that the Purchaser shall sell the shares of Common Stock purchased hereunder only to institutional investors.

Section IV.5 Compliance with Laws.

(a) The Company shall comply, and cause each subsidiary to comply, with all applicable laws, rules, regulations and orders, noncompliance with which could have a Material Adverse Effect.

(b) The Company will not be obligated to issue and the Purchaser will not be obligated to purchase any shares of the Company's Common Stock which would result in the issuance under this Agreement of more than nineteen and nine-tenths percent (19.9%) of the issued

and outstanding shares of the Company's Common Stock.

Section IV.6 Keeping of Records and Books of Account. The Company shall keep and cause each subsidiary to keep adequate records and books of account, in which complete entries will be made in accordance with GAAP consistently applied, reflecting all financial transactions of the Company and its subsidiaries, and in which, for each fiscal year, all proper reserves for depreciation, depletion, obsolescence, amortization, taxes, bad debts and other purposes in connection with its business shall be made.

Section IV.7 Reporting Requirements. Upon request, the Company shall furnish the following to the Purchaser so long as such Purchaser shall be obligated hereunder to purchase Shares:

(a) Quarterly Reports filed with the Commission on Form 10-Q as soon as available, and in any event within 47 days after the end of each of the first three fiscal quarters of the Company; and

(b) Annual Reports filed with the Commission on Form 10-K as soon as available, and in any event within 92 days after the end of each fiscal year of the Company.

Section IV.8 Intentionally Omitted.

Section IV.9 Other Agreements. The Company shall not enter into any agreement in which the terms of such agreement would (i) restrict or impair the right to perform of the Company or any subsidiary under this Agreement or the Articles of the Company, or (ii) cause the Company to issue any Common Stock or securities convertible into Common Stock during a Draw Down Pricing Period under this Agreement. If, the Company enters into any equity financing facility which will result in the issuance of the Company's Common Stock, excluding any equity financing facility (including securities convertible into common stock) in conjunction with a strategic corporate partnering transaction, without the Purchaser's prior written consent, which consent shall not be unreasonably withheld, the Purchaser may, at its option, terminate this Agreement or abstain from accepting a Draw Down Request under this Agreement for a period of three consecutive months.

Section IV.10 Effective Registration Statement. If, at the time this Agreement is executed and delivered, it is necessary for the Registration Statement or a post-effective amendment thereto to be declared effective before the offering of the Shares may commence, the Company will endeavor to cause the Registration Statement or such post-effective amendment to become effective as soon as reasonably practicable and will advise you promptly and, if requested by the Purchaser, will confirm such advice in writing, when it receives notice that the Registration Statement or such post-effective amendment has become effective.

Section IV.11 No Stop Orders. The Company will advise the Purchaser promptly and, if requested by the Purchaser, will confirm such advice in writing: (i) of its receipt of notice of any request by the Commission for amendment of or a supplement to the Registration Statement, any Prospectus or for additional information; (ii) of its receipt of notice of the issuance by the Commission of any stop order suspending the effectiveness of the Registration Statement or of the suspension of qualification of the Shares for offering or sale in any jurisdiction or the initiation of any proceeding for such purpose; and (iii) of its becoming aware of the happening of any event, which makes any statement of a material fact made in the Registration Statement or the Prospectus (as then amended or supplemented) untrue or which requires the making of any additions to or changes in the Registration Statement or the Prospectus (as then amended or supplemented) in order to state a material fact required by the Securities Act or the regulations thereunder to be stated therein or necessary in order to make the statements therein not misleading, or of the necessity to amend or supplement the Prospectus (as then amended or supplemented) to comply with the Securities Act or any other law. If at any time the Commission shall issue any stop order suspending the effectiveness of the Registration Statement, the Company will make commercially reasonable efforts to obtain the withdrawal of such order at the earliest possible time.

Section IV.12 Intentionally Omitted.

Section IV.13 Amendments to the Registration Statement. The Company will not (i) file any amendment to the Registration Statement or make any amendment or supplement to the Prospectus of which the Purchaser shall not previously have been advised or to which the Purchaser shall reasonably object after being so advised or (ii) so long as, in the reasonable opinion of counsel for the Purchaser, a Prospectus is required to be delivered in connection with sales by any Purchaser or dealer, file any information, documents or reports pursuant to the Exchange Act without delivering a copy of such information, documents or reports to the Purchaser, promptly following such filing.

Section IV.14 Prospectus Delivery. Prior to the execution and delivery of this Agreement, the Company will deliver to the Purchaser, without charge, in such quantities as reasonably requested by the Purchaser, copies of each form of Prospectus. As soon after the execution and delivery of this Agreement as possible and thereafter from time to time for such period as in the opinion of counsel for the Purchasers a prospectus is required by the Securities Act to be delivered in connection with sales by the Purchaser, the Company will expeditiously deliver to the Purchaser, without charge, as many copies of the Prospectus (and of any amendment or supplement thereto) as the Purchaser may reasonably request. The Company consents to the use of the Prospectus (and of any amendment or supplement thereto) in accordance with the provisions of the Securities Act and with the securities or Blue Sky laws of the jurisdictions in which the Shares may be sold by the Purchaser, in connection with the offering and sale of the Shares and for such period of time thereafter as the Prospectus is required by the Securities Act to be delivered in connection with sales of the Shares. If during such period of time any event shall occur that in the judgment of the Company or in the opinion of counsel for the Purchasers is required to be set forth in the Prospectus (as then amended or supplemented) or should be set forth therein in order to make the statements therein, in the light of the circumstances under which they were made, not misleading, or if it is necessary to supplement or amend the Prospectus to comply with the Securities Act or any other law, the Company will forthwith prepare and, subject to the provisions of paragraph (d) above, file with the Commission an appropriate supplement or amendment thereto, and will expeditiously furnish to the Purchaser a reasonable number of copies thereof.

Section IV.15 No Shorting. During the term of this Agreement, neither the Purchaser nor any affiliates of the Purchaser will ever be in a net short position with regard to shares of the Company's Common Stock in any account directly or indirectly managed by the Purchaser or by any affiliate of the Purchaser.

ARTICLE V

CONDITIONS TO CLOSING AND DRAW DOWNS

Section V.1 Conditions Precedent to the Obligation of the Company to Sell the Shares. The obligation hereunder of the Company to issue and sell the Shares to the Purchaser is subject to the satisfaction or waiver, at or before the Closing and with respect to each Draw Down and Call Option, of each of the conditions set forth below. These conditions are for the Company's sole benefit and may be waived by the Company at any time in its sole discretion.

(a) Accuracy of the Purchaser's Representations and Warranties. The representations and warranties of the Purchaser shall be true and correct in all material respects as of the date when made and as of the Closing as though made at that time, except for representations and warranties that are expressly made as of a particular date.

(b) Effective Registration Statement. The Registration Statement registering the

Shares shall have been declared effective by the Commission and shall have been amended or supplemented, as required, to disclose the sale of the Shares prior to the Closing Date or each Settlement Date, as applicable.

(c) Performance by the Purchaser. The Purchaser shall have performed, satisfied and complied in all material respects with all covenants, agreements and conditions required by this Agreement to be performed, satisfied or complied with by the Purchaser at or prior to the Closing.

(d) No Injunction. No statute, regulation, executive order, decree, ruling or injunction shall have been enacted, entered, promulgated or endorsed by any court or governmental authority of competent jurisdiction which prohibits the consummation of any of the transactions contemplated by this Agreement.

(e) No Suspension, Etc. Trading in the Company's Common Stock shall not have been suspended by the Commission or the NASD (except for any suspension of trading of limited duration agreed to by the Company, which suspension shall be terminated prior to Closing), and, at any time prior to the Closing, trading in securities generally as reported on NASDAQ shall not have been suspended or limited, or minimum prices shall not have been established on securities whose trades are reported by American Stock Exchange, or on the New York Stock Exchange, nor shall a banking moratorium have been declared either by the United States or New York State authorities, nor shall there have occurred any material outbreak or escalation of hostilities or other national or international calamity or crisis of such magnitude in its effect on, or any material adverse change in any financial market which, in each case, in the judgment of the Company, makes it impracticable or inadvisable to issue the Shares.

(f) No Proceedings or Litigation. No action, suit or proceeding before any arbitrator or any governmental authority shall have been commenced, and no investigation by any governmental authority shall have been threatened, against the Company or any subsidiary, or any of the officers, directors or affiliates of the Company or any subsidiary seeking to restrain, prevent or change the transactions contemplated by this Agreement, or seeking damages in connection with such transactions.

Section V.2 Conditions Precedent to the Obligation of the Purchaser to Close. The obligation hereunder of the Purchaser to enter this Agreement is subject to the satisfaction or waiver, at or before the Closing, of each of the conditions set forth below. These conditions are for the Purchaser's sole benefit and may be waived by the Purchaser at any time in its sole discretion.

(a) Accuracy of the Company's Representations and Warranties. Each of the representations and warranties of the Company shall be true and correct in all material respects as of the date when made and as of the Closing as though made at that time (except for representations and warranties that speak as of a particular date).

(b) Effective Registration Statement. The Registration Statement registering the

Shares shall have been declared effective by the Commission and shall have been amended or supplemented, as required, to disclose the sale of the Shares prior to the Closing Date or each Settlement Date, as applicable.

(c) Performance by the Company. The Company shall have performed, satisfied and complied in all material respects with all covenants, agreements and conditions required by this Agreement to be performed, satisfied or complied with by the Company at or prior to the Closing.

(d) No Suspension, Etc. Trading in the Company's Common Stock shall not have been suspended by the Commission or the NASD (except for any suspension of trading of limited duration agreed to by the Company, which suspension shall be terminated prior to Closing), and, at any time prior to the Closing, trading in securities generally as reported on NASDAQ shall not have been suspended or limited, or minimum prices shall not have been established on securities whose trades are reported by the American Stock Exchange, or on the New York Stock Exchange, nor shall a banking moratorium have been declared either by the United States or New York State authorities, nor shall there have occurred any material outbreak or escalation of hostilities or other national or international calamity or crisis of such magnitude in its effect on, or any material adverse change in any financial market which, in each case, in the judgment of the Purchaser, makes it impracticable or inadvisable to purchase the Shares.

(e) No Injunction. No statute, rule, regulation, executive order, decree, ruling or injunction shall have been enacted, entered, promulgated or endorsed by any court or governmental authority of competent jurisdiction which prohibits the consummation of any of the transactions contemplated by this Agreement.

(f) No Proceedings or Litigation. No action, suit or proceeding before any arbitrator or any governmental authority shall have been commenced, and no investigation by any governmental authority shall have been threatened, against the Company or any subsidiary, or any of the officers, directors or affiliates of the Company or any subsidiary seeking to restrain, prevent or change the transactions contemplated by this Agreement, or seeking damages in connection with such transactions.

(g) Opinion of Counsel, Etc. At the Closing, the Purchaser shall have received an opinion of counsel to the Company, dated the date of Closing, in the form of Exhibit B hereto, and such other certificates and documents as the Purchaser or its counsel shall reasonably require incident to the Closing.

Section V.3 Conditions Precedent to the Obligation of the Purchaser to Accept a Draw Down and Purchase the Shares. The obligation hereunder of the Purchaser to accept a Draw Down request and to acquire and pay for the Shares is subject to the satisfaction or waiver, at or before each Draw Down Exercise Date, of each of the conditions set forth below. The conditions are for the Purchaser's sole benefit and may be waived by the Purchaser at any time in its sole discretion.

(a) Accuracy of the Company's Representations and Warranties. Each of the representations and warranties of the Company shall be true and correct in all material respects as of the date when made and as of the Draw Down Exercise Date as though made at that time (except for representations and warranties that speak as of a particular date).

(b) Effective Registration Statement. The Registration Statement registering the Shares shall have been declared effective by the Commission and shall have been amended or supplemented, as required, to disclose the sale of the Shares prior to the Closing Date or each Settlement Date, as applicable.

(c) No Suspension. Trading in the Company's Common Stock shall not have been suspended by the Commission or the NASD (except for any suspension of trading of limited duration agreed to by the Company, which suspension shall be terminated prior to each Draw Down request), and, at any time prior to such request, trading in securities generally as reported by the American Stock Exchange shall not have been suspended or limited, or minimum prices shall not have been established on securities whose trades are reported by the American Stock Exchange.

(d) Material Adverse Effect; Material Change in Ownership. No Material Adverse Effect and no Material Change in Ownership shall have occurred.

Section V.4 Conditions Precedent to the Obligation of the Company to Issue Shares Upon Exercise of a Call Option. The obligation hereunder of the Company to issue Shares upon the exercise of a Call Option by the Purchaser is subject to the satisfaction or waiver, at or before each Settlement Date, of each of the conditions set forth below. The conditions are for the Company's sole benefit and may be waived by the Company at any time in its sole discretion.

(a) Accuracy of the Purchaser's Representations and Warranties. Each of the representations and warranties of the Purchaser shall be true and correct in all material respects as of the date when made and as of the Draw Down Exercise Date as though made at that time (except for representations and warranties that speak as of a particular date).

(b) Effective Registration Statement. The Registration Statement registering the Shares shall have been declared effective by the Commission and shall have been amended or supplemented, as required, to disclose the sale of the Shares prior to each Settlement Date.

ARTICLE VI

DRAW DOWN TERMS; CALL OPTION

Section VI.1 Draw Down Terms. Subject to the satisfaction of the conditions set forth in this Agreement, the parties agree as follows:

(a) The Company, may, in its sole discretion, issue and exercise a draw down of up to $3,000,000 (a "Draw Down") during each Draw Down Pricing Period, which Draw Down the Purchaser will be obligated to accept.

(b) The number of Shares to be issued in connection with each Draw Down shall be equal to the sum of the quotients (for each trading day of the Draw Down Pricing Period for which the VWAP equals or exceeds the Threshold Price) of (x) 1/18th of the Draw Down Amount divided by (y) 94.50% of the VWAP (the "Draw Down Discount Price") of the Common Stock.

(c) Only one Draw Down shall be allowed in each Draw Down Pricing Period.

(d) The number of Shares purchased by the Purchaser with respect to each Draw Down shall be determined on a daily basis during each Draw Down Pricing Period and settled on a weekly basis (the "Settlement Date"). If the VWAP is less than $5.00 per share on any Settlement Date, the Purchaser shall not be obligated to fund its Draw Down obligation for the preceding week.

(e) There shall be a minimum of five (5) trading days between Draw Downs.

(f) There shall be a maximum of twenty-four (24) monthly Draw Downs during the term of this Agreement.

(g) At the end of each Draw Down Pricing Period, the Purchaser's total Draw Down commitment shall be reduced by $3,000,000 regardless of the Draw Down Amount requested by the Company.

(h) Each Draw Down will expire on the last trading day of each Draw Down Pricing Period.

(i) If the VWAP on a given trading day is less than the Threshold Price, then the total amount of the Draw Down will be reduced by 1/18th and no Shares will be purchased or sold with respect to such trading day. At no time shall the Threshold Price be set below $5.00 unless agreed upon by the Company and the Purchaser. If trading in the Company's Common Stock is suspended for any reason for more than three (3) hours in any trading day, the price of the Common Stock shall be deemed to be below the Threshold Price for that trading day.

(j) The Company must inform the Purchaser via facsimile transmission as to the Draw Down Amount the Company wishes to exercise before commencement of trading on the first trading day of the Draw Down Pricing Period (the "Draw Down Notice"). In addition to the Draw Down Amount, the Company shall set the Threshold Price with each Draw Down Notice and shall designate the first trading day of the Draw Down Pricing Period. At no time shall the Purchaser be required to purchase more than $3,000,000 of the Company's Common Stock for a given Draw Down Pricing Period (excluding the Company's Common Stock purchased pursuant to a Call Option) so that if the Company chooses not to exercise the Draw Down in a given Draw Down Pricing Period the Purchaser is not obligated to purchase more than $3,000,000 in a subsequent Draw Down Pricing Period.

(k) With respect to any Draw Down, if the Threshold Price is set below $9.50, the Draw Down Discount Price shall be reduced to 94.125% of the VWAP and the Call Option Discount Price (as defined in Section 6.2) shall be reduced to 95.125% of the VWAP. With respect to any Draw Down, if the Threshold Price is set below $7.50, the maximum Draw Down Amount shall be reduced to $2,000,000, the Draw Down Discount Price shall be 94.125% and the Call Option Discount Price shall be reduced to 94.25%.

(l) The Purchaser shall not sell on any trading day during a Draw Down Period shares of Common Stock in excess of the quotient of (A) the sum of (x) 1/18 of the applicable Draw Down Amount and (y) the amount of any Call Option exercised by the Purchaser for such trading day divided by (B) the VWAP on such trading day.

(m) On each Settlement Date, the Company shall deliver the Shares purchased by the Purchaser to the Purchaser or to The Depositary Trust Company ("DTC") on the Purchaser's behalf. The Company and the Purchaser shall cause such Shares to be credited to the DTC account designated by the Purchaser upon receipt by the Company of payment for the Draw Down into an account designated by the Company. The delivery of the shares of Common Stock into the Purchaser's DTC account in exchange for payment therefor shall be referred to herein as "Settlement". The Purchaser shall coordinate Settlement with the Company through DTC.

Section VI.2 Purchaser's Call Option.

(a) The Purchaser shall have the right to exercise multiple call options during each Draw Down Pricing Period (a "Call Option"); provided, that each Call Option shall be for a minimum of $50,000 and all Call Options exercised during a Draw Down Pricing Period may not exceed $3,000,000; provided, further, that in no event shall the Purchaser exercise a Call Option for an amount which will exceed twenty percent (20%) of the Total Value on the day the applicable Call Option Notice is issued.

(b) The number of shares of Common Stock to be issued in connection each Call Option shall be based on a price of 95.50% of the VWAP (the "Call Option Discount Price") for the Common Stock on the day the Purchaser issues its Call Option Notice and shall be

determined in accordance with Section 6.1 (b) and shall not be less than the Threshold Price.

(c) Each Call Option exercised shall be settled on a weekly basis on the next Settlement Date. If the VWAP is less than $5.00 per share on any Settlement Date, the Purchaser shall not be obligated to fund its Call Option obligation for such preceding week.

(d) The Threshold Price designated by the Company in its Draw Down Notice shall apply to each Call Option.

(e) For each Call Option that the Purchaser exercises pursuant to this Section, the Purchaser must issue a Call Option Notice to the Company no later than 5:00 p.m. (New York time) on the day such Call Option is exercised. If the Purchaser does not exercise a Call Option by 5:00 p.m. (New York time) on the last day of the applicable Draw Down Pricing Period, the Purchaser's Call Options with respect to that Draw Down Pricing Period shall terminate.

(f) During the period from the Effective Date and the date which is the fourteenth (14th) month anniversary of the Effective Date (the "First Call Option Period"), the Purchaser will exercise Call Options for an aggregate amount equal to at least the product of (i) $10,000,000 multiplied by (ii) the fraction, the numerator of which is the total of all Draw Down Amounts during the First Call Option Period and the denominator of which is $36,000,000. During the period commencing after the end of the First Call Option Period and ending on the date which is the twenty-eighth (28th) month anniversary of the Effective Date (the "Second Call Option Period"), the Purchaser will exercise Call Options for an aggregate amount equal to at least the product of (A) $8,000,000 multiplied by (B) the fraction, the numerator of which is the total of all Draw Down Amounts during the Second Call Option Period and the denominator of which is $36,000,000.

ARTICLE VII

TERMINATION

Section VII.1 Termination by Mutual Consent. The term of this Agreement shall be twenty eight (28) months from the Effective Date. This Agreement may be terminated at any time by mutual consent of the parties.

Section VII.2 Other Termination. The Purchaser may terminate this Agreement upon (x) one (1) day's notice if the Company issues convertible debentures or enters an equity financing facility as set forth in Section 4.9 without the Purchaser's prior written consent, or (y) ten (10) days' notice if an event resulting in a Material Adverse Effect or a Material Change of Control in Ownership has occurred. In addition, the Company may terminate this Agreement on one (1) day's notice (which notice may not be given during a Draw Down Pricing Period); provided, that the Company pays any fee which is otherwise payable pursuant to Section 9.1(b) upon such termination if such termination occurs prior to the eighth month anniversary of the Closing.

Section VII.3 Effect of Termination. In the event of termination by the Company or the Purchaser, written notice thereof shall forthwith be given to the other party and the transactions contemplated by this Agreement shall be terminated without further action by either party. If this Agreement is terminated as provided in Section 7.1 or 7.2 herein, this Agreement shall become void and of no further force and effect, except as provided in Section 9.10. Nothing in this Section 7.3 shall be deemed to release the Company or the Purchaser from any liability for any breach under this Agreement, or to impair the rights of the Company and the Purchaser to compel specific performance by the other party of its obligations under this Agreement.

ARTICLE VIII

INDEMNIFICATION

Section VIII.1General Indemnity

(a) Indemnification by the Company. The Company will indemnify and hold harmless the Purchaser and each person, if any, who controls the Purchaser within the meaning of Section 15 of the Securities Act or Section 20(a) of the Exchange Act from and against any losses, claims, damages, liabilities and expenses (including reasonable costs of defense and investigation and all attorney's fees) to which the Purchaser and each person, if any, who controls the Purchaser may become subject, under the Securities Act or otherwise, insofar as such losses, claims, damages, liabilities and expenses (or actions in respect thereof) arise out of or are based upon, (i) any untrue statement or alleged untrue statement of a material fact contained, or incorporated by reference, in the Registration Statement relating to Common Stock being sold to the Purchaser (including the Prospectus dated _____, 1999, the Prospectus Supplement dated _____ (the "Prospectus Supplement") which are a part of it), or any amendment or supplement to it, or (ii) the omission or alleged omission to state in that Registration Statement or any document incorporated by reference in the Registration Statement, a material fact required to be stated therein or necessary to make the statements therein not misleading.

The Company will reimburse the Purchaser and each such controlling person promptly upon demand for any legal or other costs or expenses reasonably incurred by or the controlling person in investigating, defending against, or preparing to defend against any such claim, action, suit or proceeding, except that the Company will not be liable to the extent a claim or action which results in a loss, claim, damage, liability or expense arises out of, or is based upon, an untrue statement, alleged untrue statement, omission or alleged omission, included in any Prospectus or Prospectus Supplement or any amendment or supplement to the Prospectus or Prospectus Supplement in reliance upon, and in conformity with, written information furnished by the Purchase to the Company for inclusion in the Prospectus or Prospectus Supplement.

(b) Indemnification by the Purchaser. The Purchaser will indemnify and hold harmless the Company, each of its directors and officers, and each person, if any, who controls the

Company within the meaning of Section 15 of the Securities Act or Section 20(a) of the Exchange Act from and against any expenses (including reasonable costs of defense and investigation and all attorneys fees) to which the Purchaser and each person, if any, who controls the Purchaser may become subject, under the Securities Act or otherwise, insofar as such losses, claims, damages, liabilities and expenses (or actions in respect thereof) arise out of or are based upon, (i) any untrue statement or alleged untrue statement of a material fact contained in any Prospectus or Prospectus Supplement or any amendment or supplement to it or (ii) the omission or alleged omission to state in any Prospectus or Prospectus Supplement or any amendment or supplement to it a material fact required to be stated therein or necessary to make the statements therein not misleading, to the extent, but only to the extent, the untrue statement, alleged untrue statement, omission or alleged omission was made in reliance upon, and in conformity with, written information furnished by the Purchaser to the Company for inclusion in the Prospectus or Prospectus Supplement or an amendment or supplement to it, and the Purchaser will reimburse the Company and each such director, officer or controlling person promptly upon demand for any legal or other costs or expenses reasonably incurred by the Company or the other person in investigating, defending against, or preparing to defend against any such claim, action, suit or proceeding.

Section VIII.2Indemnification Procedures. Promptly after a person receives notice of a claim or the commencement of an action for which the person intends to seek indemnification under paragraph (a) or (b) of Section 8.1, the person will notify the indemnifying party in writing of the claim or commencement of the action, suit or proceeding, but failure to notify the indemnifying party will not relieve the indemnifying party from liability under paragraph (a) or (b) of Section 8.1, except to the extent it has been materially prejudiced by the failure to give notice. The indemnifying party will be entitled to participate in the defense of any claim, action, suit or proceeding as to which indemnification is being sought, and if the indemnifying party acknowledges in writing the obligation to indemnify the party against whom the claim or action is brought, the indemnifying party may (but will not be required to) assume the defense against the claim, action, suit or proceeding with counsel satisfactory to it. After an indemnifying party notifies an indemnified party that the indemnifying party wishes to assume the defense of a claim, action, suit or proceeding the indemnifying party will not be liable for any legal or other expenses incurred by the indemnified party in connection with the defense against the claim, action, suit or proceeding except that if, in the opinion of counsel to the indemnifying party, one or more of the indemnified parties should be separately represented in connection with a claim, action, suit or proceeding the indemnifying party will pay the reasonable fees and expenses of one separate counsel for the indemnified parties. Each indemnified party, as a condition to receiving indemnification as provided in Paragraph (a) or (b) or Section 8.1, will cooperate in all reasonable respects with the indemnifying party in the defense of any action or claim as to which indemnification is sought. No indemnifying party will be liable for any settlement of any action effected without its prior written consent. No indemnifying party will, without the prior written consent of the indemnified party, effect any settlement of a pending or threatened action with respect which an indemnified party is, or is informed that it may be, made a party and for which it would be entitled to indemnification, unless the settlement includes an unconditional release of the indemnified party from all liability and claims which are the subject matter of the pending or threatened action.

If for any reason the indemnification provided for in this Agreement is not available to, or is not sufficient to hold harmless, an indemnified party in respect of any loss or liability referred to in paragraph (a) or (b) of Section 8.1, each indemnifying party will, in lieu of indemnifying the indemnified party, contribute to the amount paid or payable by the indemnified party, contribute to the amount paid or payable by the indemnified party as a result of the loss or liability, (i) in the proportion which is appropriate to reflect the relative benefits received by the indemnifying party on the one hand and by the indemnified party on the other from the sale of stock which is the subject of the claim, action, suit or proceeding which resulted in the loss or liability or (ii) if that allocation is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits of the sale of stock, but also the relative fault of the indemnifying party and the indemnified party with respect to the statements or omissions which are the subject of the claim, action, suit or proceeding that resulted in the loss or liability, as well as any other relevant equitable considerations.

ARTICLE IX

MISCELLANEOUS

Section IX.1 Fees and Expenses.

(a) The Company shall pay the Purchaser a fee equal to one-quarter of one percent (0.25%) of each Draw Down Amount and the amount of each Call Option, which fee shall be paid on each Settlement Date.

(b) The Company shall pay all reasonable fees and expenses related to the transactions contemplated by this Agreement; provided, that the Company shall pay, at the Closing, all reasonable attorneys fees and expenses (exclusive of disbursements and out-of-pocket expenses) incurred by the Purchaser up to $50,000 in connection with the preparation, negotiation, execution and delivery of this Agreement. In addition, the Company shall pay all reasonable fees and expenses incurred by the Purchaser in connection with any amendments, modifications or waivers of this Agreement or incurred in connection with the enforcement of this Agreement, including, without limitation, all reasonable attorneys fees and expenses. The Company shall pay all stamp or other similar taxes and duties levied in connection with issuance of the Shares pursuant hereto.

(c) If on the twelve (12) month anniversary of the Closing Date, the Company has not requested Draw Downs in an aggregate amount of at least $24,000,000, the Company, at its option, shall pay the Purchaser a fee (the "Fee") equal to either (x) $300,000, in cash, or (y) issue three-year warrants to purchase 300,000 shares of the Company's Common Stock at an exercise price of 110% of the VWAP of the Common Stock on the date of issuance. However, if the Purchaser has terminated this Agreement prior to the twelve (12) month anniversary of the Closing Date, the Company will not be required to pay any portion of this Fee.

Section IX.2 Specific Enforcement, Consent to Jurisdiction.

(a) The Company and the Purchaser acknowledge and agree that irreparable damage would occur in the event that any of the provisions of this Agreement were not performed in accordance with their specific terms or were otherwise breached. It is accordingly agreed that the parties shall be entitled to an injunction or injunctions to prevent or cure breaches of the provisions of this Agreement and to enforce specifically the terms and provisions hereof or thereof, this being in addition to any other remedy to which any of them may be entitled by law or equity.

(b) Each of the Company and the Purchaser (i) hereby irrevocably submits to the jurisdiction of the United States District Court and other courts of the United States sitting in the State of Delaware for the purposes of any suit, action or proceeding arising out of or relating to this Agreement and (ii) hereby waives, and agrees not to assert in any such suit, action or proceeding, any claim that it is not personally subject to the jurisdiction of such court, that the suit, action or proceeding is brought in an inconvenient forum or that the venue of the suit, action or proceeding is improper. Each of the Company and the Purchaser consents to process being served in any such suit, action or proceeding by mailing a copy thereof to such party at the address in effect for notices to it under this Agreement and agrees that such service shall constitute good and sufficient service of process and notice thereof. Nothing in this Section shall affect or limit any right to serve process in any other manner permitted by law.

Section IX.3 Entire Agreement; Amendment. This Agreement contains the entire understanding of the parties with respect to the matters covered hereby and, except as specifically set forth herein, neither the Company nor the Purchaser makes any representations, warranty, covenant or undertaking with respect to such matters. No provision of this Agreement may be waived or amended other than by a written instrument signed by the party against whom enforcement of any such amendment or waiver is sought.

Section IX.4 Notices. Any notice, demand, request, waiver or other communication required or permitted to be given hereunder shall be in writing and shall be effective (a) upon hand delivery, by telex (with correct answer back received), telecopy or facsimile at the address or number designated below (if delivered on a business day during normal business hours where such notice is to be received), or the first business day following such delivery (if delivered other than on a business day during normal business hours where such notice is to be received) or (b) on the second business day following the date of mailing by express courier service, fully prepaid, addressed to such address, or upon actual receipt of such mailing, whichever shall first occur. The addresses for such communications shall be:

If to the Company:	Isis Pharmaceuticals, Inc. 2292 Faraday Avenue Carlsbad, CA 92008 Telephone Number: (760) 603-2460 Fax: (760) 603-3861 Attention: B. Lynne Parshall Executive Vice President
With copies to:	Cooley Godward LLP 4365 Executive Drive Suite 1100 San Diego, California 92121 Telephone Number: (619) 550-6012 Fax: (619) 453-3555 Attention: D.B. Peck
If to the Purchaser:	Ridgeway Investment Limited Charlotte House, Charlotte Street P.O. Box N 9204 Nassau, Bahamas Telephone Number: Fax: (242) 323-7918 Attention: Mr. Anthony L. M. Inder Rieden Director and President

Any party hereto may from time to time change its address for notices by giving at least ten (10) days written notice of such changed address to the other party hereto.

Section IX.5 Waivers. No waiver by either party of any default with respect to any provision, condition or requirement of this Agreement shall be deemed to be a continuing waiver in the future or a waiver of any other provisions, condition or requirement hereof, nor shall any delay or omission of any party to exercise any right hereunder in any manner impair the exercise of any such right accruing to it thereafter.

Section IX.6 Headings. The article, section and subsection headings in this Agreement are for convenience only and shall not constitute a part of this Agreement for any other purpose and shall not be deemed to limit or affect any of the provisions hereof.

Section IX.7 Successors and Assigns. The Purchaser may not assign this Agreement to any person without the prior consent of the Company, which consent will not be unreasonably withheld. This Agreement shall be binding upon and inure to the benefit of the parties and their successors and assigns. The parties hereto may not amend this Agreement or any rights or obligations hereunder without the prior written consent of the Company and each Purchaser to be affected by the amendment. After Closing, the assignment by a party to this Agreement of any rights hereunder shall not affect the obligations of such party under this Agreement.

Section IX.8 Governing Law. This Agreement shall be governed by and construed in accordance with the internal laws of the State of Delaware, without giving effect to the choice of law provisions.

Section IX.9 Survival. The representations and warranties of the Company and the Purchaser contained in Article III and the covenants contained in Article IV shall survive the execution and delivery hereof and the Closing until the termination of this Agreement, and the agreements and covenants set forth in Article VIII of this Agreement shall survive the execution and delivery hereof and the Closing hereunder.

Section IX.10 Counterparts. This Agreement may be executed in any number of counterparts, all of which taken together shall constitute one and the same instrument and shall become effective when counterparts have been signed by each party and delivered to the other parties hereto, it being understood that all parties need not sign the same counterpart. In the event any signature is delivered by facsimile transmission, the party using such means of delivery shall cause four additional executed signature pages to be physically delivered to the other parties within five days of the execution and delivery hereof.

Section IX.11 Publicity. Prior to the Closing, neither the Company nor the Purchaser shall issue any press release or otherwise make any public statement or announcement with respect to this Agreement or the transactions contemplated hereby or the existence of this Agreement. In the event the Company is required by law, based upon an opinion of the Company's counsel, that the Company must issue a press release or otherwise make a public statement or announcement with respect to this Agreement prior to the Closing, the Company shall consult with the Purchaser on the form and substance of such press release. After the Closing, the Company may issue a press release or otherwise make a public statement or announcement with respect to this Agreement or the transactions contemplated hereby or the existence of this Agreement; provided, that prior to issuing any such press release, making any such public statement or announcement, the Company obtains the prior consent of the Purchaser, which consent shall not be unreasonably withheld or delayed.

Section IX.12 Severability. The provisions of this Agreement are severable and, in the event that any court of competent jurisdiction shall determine that any one or more of the provisions or part of the provisions contained in this Agreement shall, for any reason, be held to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability shall not affect any other provision or part of a provision of this Agreement, and this Agreement shall be reformed and construed as if such invalid or illegal or unenforceable provision, or part of such provision, had never been contained herein, so that such provisions would be valid, legal and enforceable to the maximum extent possible.

Section IX.13 Further Assurances. From and after the date of this Agreement, upon the request of the Purchaser or the Company, each of the Company and the Purchaser shall execute and deliver such instrument, documents and other writings as may be reasonably necessary or desirable to confirm and carry out and to effectuate fully the intent and purposes of this Agreement.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed by their respective authorize officer as of the date first above written.

ISIS PHARMACEUTICALS, INC.

By:

Name:
Title

RIDGEWAY INVESTMENT LIMITED

By:

Name:
Title