AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON OCTOBER 9, 2001

REGISTRATION NO. 333-

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

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

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

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

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

B. Lynne Parshall, Esq.
Executive Vice President and Chief Financial Officer
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:

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

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

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

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

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

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

CALCULATION OF REGISTRATION FEE

TITLE OF EACH CLASS OF SECURITIES TO BE REGISTERED	AMOUNT TO BE REGISTERED(1)	PROPOSED MAXIMUM OFFERING PRICE PER SHARE(2)	PROPOSED MAXIMUM AGGREGATE OFFERING PRICE(2)	AMOUNT OF REGISTRATION FEE
Common Stock, $.001 per share.....	5,750,000	$17.78	$102,235,000	$25,559

(1) Includes 750,000 shares of our common stock which may be purchased by the Underwriters to cover over-allotments, if any.

(2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(c) of the Securities Act of 1933 based upon the average of the high and low prices of our common stock as reported on the Nasdaq National Market on October 2, 2001.

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.

PRELIMINARY PROSPECTUS SUBJECT TO COMPLETION OCTOBER 9, 2001

THE INFORMATION IN THIS PROSPECTUS IS NOT COMPLETE AND MAY BE CHANGED. WE MAY NOT SELL THESE SECURITIES UNTIL THE REGISTRATION STATEMENT FILED WITH THE SECURITIES AND EXCHANGE COMMISSION IS EFFECTIVE. THIS PROSPECTUS IS NOT AN OFFER TO SELL THESE SECURITIES AND WE ARE NOT SOLICITING OFFERS TO BUY THESE SECURITIES IN ANY STATE IN WHICH THE OFFER OR SALE IS NOT PERMITTED.

5,000,000 SHARES

[LOGO]

COMMON STOCK

We are selling all of the 5,000,000 shares of common stock offered by this prospectus.

Our common stock is quoted on the Nasdaq National Market under the symbol "ISIP." On October 8, 2001, the last reported sales price of our common stock on the Nasdaq National Market was $18.30 per share.

INVESTING IN OUR COMMON STOCK INVOLVES A HIGH DEGREE OF RISK. BEFORE BUYING ANY SHARES YOU SHOULD READ THE DISCUSSION OF MATERIAL RISKS OF INVESTING IN OUR COMMON STOCK IN "RISK FACTORS" BEGINNING ON PAGE 5 OF THIS PROSPECTUS.

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

	PER SHARE	TOTAL
Public offering price.....	$	$
Underwriting discount and commissions.....	$	$
Proceeds, before expenses, to us.....	$	$

The underwriters may also purchase from us up to an additional 750,000 shares of our common stock at the public offering price less the underwriting discount, to cover over-allotments, if any, within 30 days of the date of this

prospectus.

The underwriters are offering the shares of our common stock as described in "Underwriting."

Delivery of the shares will be made on or about , 2001.

UBS WARBURG

ROBERTSON STEPHENS

NEEDHAM & COMPANY, INC.

FORTIS SECURITIES INC.

YOU SHOULD RELY ONLY ON THE INFORMATION CONTAINED IN THIS PROSPECTUS, INCLUDING INFORMATION INCORPORATED BY REFERENCE. WE HAVE NOT AUTHORIZED ANYONE ELSE TO PROVIDE YOU WITH DIFFERENT INFORMATION. YOU SHOULD NOT ASSUME THAT THE INFORMATION IN THIS PROSPECTUS IS ACCURATE AS OF ANY DATE OTHER THAN THE DATE ON THE FRONT OF THIS PROSPECTUS OR THAT ANY DOCUMENT INCORPORATED BY REFERENCE IS ACCURATE AS OF ANY DATE OTHER THAN ITS FILING DATE. YOU SHOULD NOT CONSIDER THIS PROSPECTUS TO BE AN OFFER OR SOLICITATION RELATING TO THE SECURITIES IN ANY JURISDICTION IN WHICH SUCH AN OFFER OR SOLICITATION RELATING TO THE SECURITIES IS NOT AUTHORIZED. FURTHERMORE, YOU SHOULD NOT CONSIDER THIS PROSPECTUS TO BE AN OFFER OR SOLICITATION RELATING TO THE SECURITIES IF THE PERSON MAKING THE OFFER OR SOLICITATION IS NOT QUALIFIED TO DO SO, OR IF IT IS UNLAWFUL FOR YOU TO RECEIVE SUCH AN OFFER OR SOLICITATION.

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ISIS PHARMACEUTICALS-TM-, GENETROVE-TM- AND IBIS THERAPEUTICS-TM- ARE TRADEMARKS OF ISIS. VITRAVENE-REGISTERED TRADEMARK- IS A REGISTERED TRADEMARK OF NOVARTIS AG. THIS PROSPECTUS ALSO CONTAINS TRADEMARKS AND SERVICEMARKS OF OTHER COMPANIES.

PROSPECTUS SUMMARY

THIS SUMMARY HIGHLIGHTS SELECTED INFORMATION APPEARING ELSEWHERE IN THIS PROSPECTUS AND MAY NOT CONTAIN ALL OF THE INFORMATION THAT IS IMPORTANT TO YOU. THIS PROSPECTUS INCLUDES INFORMATION ABOUT THE SHARES WE ARE OFFERING, AS WELL AS INFORMATION REGARDING OUR BUSINESS AND DETAILED FINANCIAL DATA. WE ENCOURAGE YOU TO READ THIS PROSPECTUS IN ITS ENTIRETY, INCLUDING THE DOCUMENTS INCORPORATED BY REFERENCE. AS USED IN THIS PROSPECTUS, UNLESS OTHERWISE SPECIFIED OR THE CONTEXT REQUIRES OTHERWISE, THE TERMS "ISIS," "WE," "OUR" AND "US" REFER TO ISIS PHARMACEUTICALS, INC.

BUSINESS OVERVIEW

We are a biopharmaceutical company pioneering RNA-based drug discovery technologies to identify and commercialize novel drugs to treat significant unmet medical needs. RNA, or ribonucleic acid, is a molecule that provides to a cell the information needed to produce proteins, some of which are involved in disease. Interference with RNA can keep proteins involved in disease from being produced. We have strong proprietary positions in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors

designed to bind with high specificity to their intended RNA target. With our Ibis technology, we use our expertise in RNA to design small molecule therapeutics that interfere with RNA. We also use our antisense technology in collaborations with pharmaceutical company partners to identify and prioritize attractive gene targets for their drug discovery programs. We believe we have established a leadership position in exploiting RNA as a target for therapeutic intervention.

We have used our antisense technology to commercialize our first product, Vitravene. Vitravene demonstrates our ability to meet FDA regulatory requirements and to commercially manufacture antisense drugs. We have 12 products in our development pipeline with eight in human clinical trials designed to assess efficacy. Our products in development address numerous therapeutic areas with major market potential, including cancer, psoriasis, rheumatoid arthritis, hepatitis C and diabetes. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient compliance and convenience. We are also pursuing second-generation drugs that may be able to be dosed as infrequently as once per month and that may be able to be dosed orally.

ISIS 3521, our most advanced product currently under development, is undergoing Phase III clinical trials in combination with traditional chemotherapy cancer drugs. We initiated this Phase III trial in late 2000 for patients with non-small cell lung cancer, the most common form of lung cancer, based on promising results in patients in the Phase II trial. Results from this study showed a median survival time of 15.9 months in patients using our drug in combination with standard chemotherapy. The typical median survival time of similar cancer patients receiving standard chemotherapy alone is approximately seven or eight months. In November 2000, the FDA granted ISIS 3521 fast track review status. Prior to the end of 2001, we also plan to initiate Phase III clinical trials for another product, ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. We have five additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide pharmaceutical companies with important information about genes that these companies are interested in targeting for their drug discovery programs. We provide this information rapidly and efficiently, using the same proprietary methods and systems that we developed to create antisense drugs. We have collaborations in place with five major pharmaceutical partners for these services, including Eli Lilly and Company, Celera Genomics Group, Abbott Laboratories Inc., Aventis (Rhone-Poulenc Rorer) and the R.W. Johnson Pharmaceutical Research Institute, a member of the Johnson & Johnson family of companies. We have supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product in August 2001. This database is expected to contain proprietary information about the function of thousands of genes, which we believe pharmaceutical

companies will find valuable in designing and prioritizing their drug discovery programs. Our GeneTrove division is generating near-term revenues while enhancing our own antisense drug discovery efforts and our patent portfolio.

Our Ibis Therapeutics division designs small molecule drugs that work by binding to RNA, in contrast to traditional drugs, which bind to proteins. Our scientists have invented methods of identifying RNA targets and screening for drugs which bind to RNA. Since its inception, Ibis has received significant financial support from various federal government agencies to use its technology for the development of RNA-based countermeasures to biological warfare. In June 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a Pfizer company, in a research partnership worth up to $37 million. In May 2001, we received a $2.5 million milestone payment under this collaboration.

We have a broad patent portfolio relating to our technologies. We own or have an exclusive license to more than 800 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset of the company. We are exploiting our patent estate to generate near-term revenues for the company.

RECENT DEVELOPMENTS

ELI LILLY AND COMPANY. In August 2001, we entered into a broad strategic relationship with Lilly that has four key components:

- Lilly purchased $75 million of our common stock at $18 per share.

- We licensed to Lilly rights to ISIS 3521, our antisense drug in Phase III trials for the treatment of non-small cell lung cancer.

- We initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related GeneTrove collaboration to determine the function of up to 1,000 genes.

- Lilly committed to lend us, interest-free, up to $100 million over a four-year period to fund our obligations under the drug discovery collaboration. This loan is repayable at our option in either cash or our common stock, valued at $40 per share.

If this collaboration is successful, the cumulative contingent funds over the life of the development process have the potential to exceed these committed funds.

MERCK & CO., INC. In May 2001, we licensed to Merck our preclinical antisense drug candidate, ISIS 113715, for adult onset, or Type 2, diabetes. Under the agreement, Merck has agreed to develop and commercialize ISIS 113715 in exchange for an upfront fee and milestone payments and royalties upon its successful development and approval. In August 2001, we received a $2 million milestone payment under this agreement.

CELERA GENOMICS GROUP. In July 2001, Celera and our GeneTrove division entered into a collaboration to identify the biological role of more than 200 genes. Celera has the right to select for study a portfolio of genes, from which Celera can further select a limited number of genes for their exclusive use. The data for the remainder of the genes will be included in our human gene function database. We retain the rights to develop and commercialize antisense drugs to genes in the collaboration. Celera has agreed to pay us fees for this 18-month collaboration.

THE OFFERING

Common Stock offered.....	5,000,000 shares
Common Stock outstanding after the offering.....	52,087,796 shares
Use of proceeds.....	For research, drug discovery and development activities, including preclinical and clinical studies, production of compounds for studies, capital expenditures, and other general corporate purposes. See "Use of Proceeds."
Nasdaq National Market symbol.....	ISIP

Unless we specifically state otherwise, the information in this prospectus assumes that the underwriters do not exercise their option to purchase up to 750,000 shares of common stock to cover over-allotments.

The number of shares of our common stock to be outstanding after the offering in the table above is based on the number of shares outstanding as of September 30, 2001, and does not include, as of that date:

- 8,443,801 shares of our common stock issuable upon exercise of outstanding options issued under our equity incentive plans at a weighted average exercise price of $9.47 per share and an additional 2,228,952 shares of common stock available for future grants under our equity incentive plans;

- 1,029,881 shares of our common stock issuable upon exercise of outstanding warrants at a weighted average exercise price of $25.16 per share;

- 1,562,020 shares of our common stock issuable upon conversion of our outstanding Series A and Series B Convertible Preferred Stock and related accreted dividends, assuming a stock price of $17.05 per share, the closing price of our common stock on September 30, 2001;

- 3,007,182 shares of our common stock issuable upon the conversion of our outstanding indebtedness assuming a stock price of $17.05 per share, the closing price of our common stock on September 30, 2001; and

- shares of our common stock issuable to Hybridon, with a maximum of 2,071,429 shares and a minimum of 673,077 shares.

OTHER INFORMATION

Isis Pharmaceuticals, Inc. was incorporated in California in January 1989, and in April 1991 we changed our 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. Information contained on our website, www.isip.com, does not constitute part of this prospectus.

Our research and development programs have continued to evolve subsequent to our description of those programs in documents incorporated by reference in this prospectus. Some programs may have been deferred or abandoned, and some programs may have been added. While these changes may be material as to any particular program, we do not believe that, except as may be described herein or in a document incorporated by reference, they are material to our business overall.

SUMMARY CONSOLIDATED FINANCIAL DATA

The as adjusted balance sheet data gives effect to the sale of 5,000,000 shares of our common stock in this offering at an assumed price of $18.30 per share, after deducting the underwriting discount and estimated offering expenses. The following data should be read together with the financial statements, the related notes and other financial information included in this prospectus and incorporated herein by reference.

SIX MONTHS ENDED DECEMBER 31,	YEARS ENDED JUNE 30,					
1999	1998	1997	1996	2001	2000	1999
(UNAUDITED)						
(IN THOUSANDS, EXCEPT PER SHARE DATA)						
STATEMENT OF OPERATIONS DATA:						
Total revenues	$37,255	$33,925	$39,171	$32,722	$22,663	$12,225
$11,039						
Research and development expenses	57,014	66,413	62,200	55,940	45,653	39,059
25,985						
Net loss applicable to common stock	(54,699)	(59,645)	(42,983)	(31,066)	(26,521)	(46,532)
(33,216)						
Basic and diluted net loss per share	(1.48)	(2.08)	(1.60)	(1.17)	(1.04)	(1.15)
(0.95)						
Shares used in computing basic and diluted net loss per share	37,023	28,703	26,873	26,456	25,585	40,322
35,021						

AS OF JUNE 30, 2001	ACTUAL	AS ADJUSTED(1)
(IN THOUSANDS, UNAUDITED)		
BALANCE SHEET DATA:		
Cash, cash equivalents and short-term investments	$106,298	$191,998
Working capital	85,007	170,707
Total assets	187,528	273,228
Long-term debt and capital lease obligations, less current portion	115,666	115,666
Accumulated deficit	(357,992)	(357,992)
Stockholders' equity	45,928	131,628

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(1) The financial data above excludes shares issued and the proceeds received from the sale of such shares, subsequent to June 30, 2001, including 4,523,810 shares issued to Lilly and Hybridon and $75 million in proceeds received from Lilly.

RISK FACTORS

INVESTING IN OUR COMMON STOCK INVOLVES A HIGH DEGREE OF RISK. IN ADDITION TO THE OTHER INFORMATION IN THIS PROSPECTUS, YOU SHOULD CAREFULLY CONSIDER THE RISKS DESCRIBED BELOW BEFORE PURCHASING OUR COMMON STOCK. IF ANY OF THE FOLLOWING RISKS ACTUALLY OCCUR, OUR BUSINESS COULD BE MATERIALLY HARMED, AND OUR FINANCIAL CONDITION AND RESULTS OF OPERATIONS COULD BE MATERIALLY AND ADVERSELY AFFECTED. AS A RESULT, THE TRADING PRICE OF OUR COMMON STOCK COULD DECLINE, AND YOU MIGHT LOSE ALL OR PART OF YOUR INVESTMENT.

IF WE OR OUR PARTNERS FAIL TO OBTAIN REGULATORY APPROVAL FOR OUR PRODUCTS, WE WILL NOT BE ABLE TO SELL THEM.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates, before a drug candidate can be approved for sale. We must conduct these trials in compliance with U.S. Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies which can be time consuming and expensive, and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in such receipt could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that could have a similar negative impact.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, be approved for commercialization or will be successfully commercialized by us or our partners.

IF THE RESULTS OF CLINICAL TESTING INDICATE THAT ANY OF OUR DRUGS UNDER DEVELOPMENT ARE NOT SUITABLE FOR COMMERCIAL USE, OR IF ADDITIONAL TESTING IS REQUIRED TO DEMONSTRATE SUCH SUITABILITY, WE MAY NEED TO ABANDON ONE OR MORE OF OUR DRUG DEVELOPMENT PROGRAMS.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. Most of our resources are being applied to create safe and effective drugs for human use; any of the risks described above could prevent us from doing so. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

IF OUR PRODUCTS ARE NOT ACCEPTED BY THE MARKET, WE ARE NOT LIKELY TO GENERATE SIGNIFICANT REVENUES OR BECOME PROFITABLE.

Our success will depend upon the medical community, patients and third party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that any of our products in development, if approved for commercialization, will be used by doctors to treat patients. We currently have one commercially available product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small market. We and our partners may not be successful in commercializing additional products.

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

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;
- the cost of our drug candidates compared to other available therapies;
- the patient convenience of the dosing regimen for our drug candidates; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drug candidates, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

IF ANY OF OUR COLLABORATIVE PARTNERS FAIL TO FUND OUR COLLABORATIVE PROGRAMS OR DEVELOP OR SELL ANY OF OUR PRODUCTS UNDER DEVELOPMENT, OR IF WE ARE UNABLE TO OBTAIN ADDITIONAL PARTNERS, PROGRESS ON OUR DRUG DEVELOPMENT PROGRAMS COULD BE DELAYED OR STOP.

We have entered into collaborative arrangements with third parties to develop certain product candidates. We enter into these collaborations in order to:

- fund our research and development activities;

- access manufacturing by third parties;

- seek and obtain regulatory approvals; and

- successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may be negatively affected. We cannot be sure that any of these collaborations will be continued or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. Our most advanced drug candidate, ISIS 3521, is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners including Merck & Company, Inc. and Elan Corporation, plc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

Certain of our partners are 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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

Historically, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

IF OUR GENETROVE BUSINESS IS UNABLE TO MARKET ITS PRODUCTS AND SERVICES AS PLANNED, WE COULD LOSE OUR INVESTMENT IN THIS TECHNOLOGY.

Our business could suffer if pharmaceutical companies do not avail themselves of our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and gene functionalization service business for validation and functionalization of gene targets for drug discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance.

If we fail to introduce our human gene function database in a timely fashion or if potential customers do not subscribe to the database at the level we have planned, our GeneTrove business could fail to make the planned contribution to our financial performance.

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

Because drug discovery and development and the development of database products and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of June 30, 2001, our accumulated losses were approximately $358 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain

future profitability.

IF WE FAIL TO OBTAIN TIMELY FUNDING, WE MAY NEED TO CURTAIL OR ABANDON SOME OF OUR PROGRAMS.

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the proceeds from this offering, will be adequate to satisfy our capital needs for the foreseeable future. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- 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;
- competing technological and market developments, including the introduction of new therapies that address our markets;
- success in the marketing of our gene function database and research service products; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds we may need to raise them through public or private financing. Additional financing may not be available, at all or on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be diluted and their price 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.

IF WE CANNOT MANUFACTURE OUR PRODUCTS OR CONTRACT WITH A THIRD PARTY TO MANUFACTURE OUR PRODUCTS AT COSTS THAT ALLOW US TO CHARGE COMPETITIVE PRICES TO BUYERS, WE WILL NOT BE ABLE TO MARKET PRODUCTS PROFITABLY.

If we are successful commercializing any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. Pharmaceutical products of the chemical class represented by our drug candidates, called "oligonucleotides", have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have 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. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which are enforced by the FDA through its facilities inspection program. The manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt or marketing approval or result in FDA enforcement action.

IF WE FAIL TO COMPETE EFFECTIVELY, OUR PRODUCTS WILL NOT CONTRIBUTE SIGNIFICANT REVENUES.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in

developing antisense technology. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

Our GeneTrove division competes with others in the use of antisense technology for gene target validation and gene functionalization, as well as with other technologies useful for target validation and gene functionalization. Our competition may provide services having more value to potential customers or may market their services more effectively to such potential customers. In either case, our gene functionalization and target validation businesses may not contribute to our financial performance as planned.

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

IF WE ARE UNABLE TO PROTECT OUR PATENTS OR OUR PROPRIETARY RIGHTS, OTHERS MAY BE ABLE TO COMPETE MORE DIRECTLY AGAINST US.

Our success depends to a significant degree upon our ability to develop and secure intellectual property rights to proprietary products and services. However, patents may not be granted on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to adequately protect our competitive advantage. Furthermore, our issued patents or patents licensed to us could potentially be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

INTELLECTUAL PROPERTY LITIGATION COULD BE EXPENSIVE AND PREVENT US FROM PURSUING OUR PROGRAMS.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the US Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging infringement of U.S. Patent 6,001,653. If we do not prevail in the defense of this patent, it could impact our ability to realize future licensing revenues.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the US are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

IF WE DO NOT PROGRESS IN OUR PROGRAMS AS ANTICIPATED, OUR STOCK PRICE COULD DECREASE.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter the clinic, when a clinical trial will be completed or when an application for marketing approval will be filed. Some of our estimates are included in this prospectus. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and our stock price would likely decrease.

THE LOSS OF KEY PERSONNEL, OR THE INABILITY TO ATTRACT AND RETAIN HIGHLY SKILLED PERSONNEL, COULD MAKE IT MORE DIFFICULT TO RUN OUR BUSINESS AND REDUCE OUR LIKELIHOOD OF SUCCESS.

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. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms, because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

OUR STOCK PRICE MAY CONTINUE TO BE HIGHLY VOLATILE. THIS COULD MAKE IT HARDER FOR YOU TO LIQUIDATE YOUR INVESTMENT AND COULD INCREASE YOUR RISK OF SUFFERING A LOSS.

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 twelve months preceding September 28, 2001, the market price of our common stock has ranged from $7.875 to $18.05 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our certificate of incorporation provides for classified terms for the members of our 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, any holder of 15% or more of our voting stock, 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. We also have implemented a stockholders' rights plan, which is also called a "poison pill," which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our 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 our company without action by our stockholders.

IF REGISTRATION RIGHTS THAT WE HAVE PREVIOUSLY GRANTED ARE EXERCISED, THEN OUR STOCK PRICE MAY BE NEGATIVELY AFFECTED.

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, Hybridon, Inc. and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 5,732,273 shares of our common stock which are currently outstanding, an additional $14.5 million of our common stock we are obligated to issue to Hybridon, and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these registration rights are exercised by the holders, it will bring additional shares of our common stock into the market, which may have an adverse effect on our stock price. In addition, Reliance has registration rights with respect to the approximately $66 million of notes we issued to Reliance.

IF YOU PURCHASE OUR COMMON STOCK IN THIS OFFERING, YOU WILL INCUR IMMEDIATE AND SUBSTANTIAL DILUTION IN THE BOOK VALUE OF YOUR SHARES.

You will experience an immediate and substantial dilution of $16.47 per share in the net tangible book value per share of our common stock, assuming a public offering price of $18.30 per share. After giving effect to this offering, and to other issuances of our common stock as described in the

"Dilution" section of this prospectus, our pro forma adjusted net tangible book value as of June 30, 2001, would have been $1.83 per share. In addition, this dilution will be increased to the extent that holders of outstanding options and warrants to purchase our common stock at prices below our net tangible book value per share after this offering exercise those options or warrants.

DISCLOSURE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Such statements are subject to certain risks and uncertainties, particularly those inherent in discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation activities and in launching new products and services for or with collaborators, and the endeavor of building a business around such potential products. Actual results could differ materially from those discussed in this Prospectus. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk Factors" beginning on page 5 of this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

USE OF PROCEEDS

The net proceeds to us from the sale of the 5,000,000 shares of common stock we are offering will be approximately $85.7 million. If the underwriters exercise the over-allotment option in full, the net proceeds to us will be approximately $98.6 million. For the purpose of estimating net proceeds, we are assuming that the public offering price will be $18.30 per share. "Net proceeds" is what we expect to receive after we pay the underwriting discount and other estimated expenses for this offering.

We intend to use the net proceeds of this offering for 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 these 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 these expenditures. However, we currently plan that a portion of the proceeds will be used to support our planned research and development efforts. The remaining proceeds will be used for general corporate purposes. The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering, progress of our research, drug discovery and development programs, the results of preclinical and clinical studies, the timing of regulatory approvals, technological advances, determinations as to commercial potential of our compounds and the status of competitive products. In addition, expenditures will also depend upon the establishment of collaborative research arrangements with other companies, the availability of other financing and other factors.

We may use a portion of the net proceeds to acquire or invest in businesses, products or technologies that are complementary to our own. However, we are not currently a party to any agreement regarding a material acquisition and no portion of the net proceeds have been allocated for any specific acquisition.

Pending any of the above uses, the net proceeds will be invested in investment-grade, interest-bearing debt securities.

CAPITALIZATION

The following table sets forth our capitalization at June 30, 2001:

- on an actual basis; and
- on an as adjusted basis to give effect to the sale of the 5,000,000 shares of common stock offered by us, assuming a public offering price of $18.30 per share and after deducting underwriting discounts and commissions and estimated offering expenses to be paid by us:

(IN THOUSANDS, EXCEPT SHARE DATA)	ACTUAL	AS ADJUSTED(1)
Cash, cash equivalents and short term investments	$106,298	$191,998
Long-term debt and capital lease obligations, less current portion	$115,666	$115,666
Stockholders' equity: Series A Convertible Exchangeable 5% Preferred stock, $.001 par value; 120,150 shares authorized, issued and outstanding, actual and adjusted	12,015	12,015

Accretion of Series A Preferred stock dividends..... 1,376 1,376 Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding, actual and adjusted..... 12,015 12,015 Accretion of Series B Preferred stock dividends..... 899 899 Common stock, $.001 par value; 100,000,000 shares authorized, 42,247,956 shares issued and outstanding, actual; and 47,247,956 shares issued and outstanding, as adjusted..... 42 47 Additional paid-in capital..... 377,333 463,028 Deferred compensation..... (329) (329) Accumulated other comprehensive income..... 569 569 Accumulated deficit..... (357,992) (357,992) -------- -------- Total stockholders' equity..... 45,928 131,628 ----- --- -------- Total capitalization..... $161,594 $247,294 ======== ========

(1) The financial data above excludes shares issued and proceeds received from the sale of such shares, subsequent to June 30, 2001, including 4,523,810 shares issued to Lilly and Hybridon and $75 million in proceeds received from Lilly.

The table should be read in conjunction with our consolidated financial statements and the related notes appearing elsewhere in this prospectus.

DILUTION

Our net tangible book value as of June 30, 2001 was $978,000 or approximately $0.02 per share of common stock. Net tangible book value per share represents the amount of our tangible assets less total liabilities, divided by 42,247,956 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 this offering and the pro forma adjusted net tangible book value per share of common stock immediately after completion of this offering. After giving effect to the sale of 5,000,000 shares of common stock in this offering at an assumed public offering price of $18.30 per share and the receipt of the estimated net proceeds therefrom (after deducting estimated offering expenses), our pro forma adjusted net tangible book value as of June 30, 2001 would have been $86,678,000, or $1.83 per share, an immediate increase of $1.81 per share over the net tangible book value to existing stockholders and an immediate dilution of $16.47 per share to the adjusted net tangible book value to purchasers of common stock in this offering, as illustrated in the following table:

Assumed public offering price per share.....		$18.30
Net tangible book value per share at June 30, 2001.....	$0.02	
Increase per share attributable to new investors in this offering.....	1.81	
Pro forma adjusted net tangible book value per share after offering.....		1.83
Net tangible book value dilution per share to new investors in this offering.....		$16.47

To the extent that outstanding options and warrants are exercised, or our outstanding convertible preferred stock or convertible debt is converted, there could be further dilution to new investors.

MARKET PRICE OF COMMON STOCK

Our common stock is traded publicly through the Nasdaq National Market under the symbol "ISIP." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by the Nasdaq National Market. These prices do not include

retail markups, markdowns or commissions.

COMMON STOCK PRICE	HIGH	LOW
FISCAL YEAR ENDED DECEMBER 31, 1999		
First Quarter	$15.25	$ 8.94
Second Quarter	$12.19	$ 9.25
Third Quarter	$13.81	$ 9.16
Fourth Quarter	$17.38	$ 3.88
FISCAL YEAR ENDED DECEMBER 31, 2000		
First Quarter	$39.00	$ 5.75
Second Quarter	$16.25	$ 8.06
Third Quarter	$15.75	$10.50
Fourth Quarter	$14.75	$ 8.81
FISCAL YEAR ENDED DECEMBER 31, 2001		
First Quarter	$13.00	$ 7.97
Second Quarter	$13.17	$ 7.88
Third Quarter	$18.05	$ 9.75
Fourth Quarter (through October 8, 2001)	$18.95	$16.70

On October 8, 2001, the last reported sale price for our common stock was $18.30 per share, and there were approximately 1,054 stockholders of record of our common stock.

DIVIDEND POLICY

We have not paid any dividends and do not anticipate paying cash dividends in the foreseeable future. We currently intend to retain all available funds and any future earnings for use in the operation of our business. Under the terms of certain of our term loans, we are restricted from paying cash dividends until the loans are fully repaid.

SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data for the five years ended December 31, 2000 are derived from the audited consolidated financial statements of ISIS Pharmaceuticals, Inc. The financial data for the six-month periods ended June 30, 2001 and 2000 are derived from unaudited consolidated financial statements. The unaudited financial statements include all adjustments, consisting of normal recurring accruals, which the Company considers necessary for a fair presentation of the financial position and the results of operations for these periods. Operating results for the six months ended June 30, 2001 are not necessarily indicative of the results that may be expected for the entire year ending December 31, 2001. The data should be read in conjunction with the consolidated financial statements, the related notes, and other financial information incorporated by reference herein.

	SIX MONTHS ENDED JUNE 30,		YEARS ENDED DECEMBER 31,				
	2001	2000	2000	1999	1998	1997	1996
	(UNAUDITED)						
	(IN THOUSANDS, EXCEPT PER SHARE DATA)						
STATEMENT OF OPERATIONS DATA:							
Total revenues	$37,255	$33,925	$39,171	$32,722	$22,663	$ 12,225	$11,039
Research and development expenses	57,014	66,413	62,200	55,940	45,653	39,059	25,985
Net loss applicable to common stock	(54,699)	(59,645)	(42,983)	(31,066)	(26,521)	(46,532)	

(33,216) Basic and diluted net loss per share.....
(1.48) (2.08) (1.60) (1.17) (1.04) (1.15) (0.95) Shares used in computing basic and diluted net loss per share..... 37,023 28,703 26,873 26,456 25,585 40,322 35,021

AS OF DECEMBER 31, 2000	AS OF DECEMBER 31, 1999	AS OF DECEMBER 31, 1998	AS OF DECEMBER 31, 1997	AS OF DECEMBER 31, 1996	AS OF JUNE 30, 2001
(IN THOUSANDS) (UNAUDITED) BALANCE SHEET DATA: Cash, cash equivalents and short-term investments.....	$127,262	$ 52,839	$ 58,848	$ 86,786	$ 77,624	$ 106,298
Working capital.....	118,568	44,213	40,651	62,573	56,300	85,007
Total assets.....	183,256	103,107	96,074	117,881	101,305	187,528
Long-term debt and capital lease obligations, less current portion.....	102,254	87,254	77,724	56,452	19,864	115,666
Accumulated deficit.....	(311,460)	(256,761)	(197,116)	(154,133)	(123,067)	(357,992)
Stockholders' equity (deficit).....	66,366	869	(4,186)	34,852	58,385	45,928

UNDERWRITING

We and the underwriters for this offering named below have entered into an underwriting agreement concerning the shares being offered. Subject to conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc. and Fortis Securities Inc. are the representatives of the underwriters.

UNDERWRITERS	NUMBER OF SHARES
UBS Warburg LLC.....	
Robertson Stephens, Inc.....	
Needham & Company, Inc.....	
Fortis Securities Inc.....	
Total.....	5,000,000

If the underwriters sell more shares than the total number set forth in the table above, the underwriters have a 30-day option to buy up to 750,000 shares from us at the public offering price less the underwriting discounts and commissions to cover these sales. If any shares are purchased under this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table provides information regarding the amount of the discount to be paid to the underwriters by us:

NO EXERCISE	FULL EXERCISE
-- Per share.....	
$	$
Total.....	
$	$

We estimate that the total expenses of this offering payable by us, excluding underwriting discounts and commissions, will be about $310,000.

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $ per share from the public offering price. Any of these securities dealers may resell any shares purchased from the underwriters to other brokers or dealers at a discount of up to $ per share from the public offering price. If all the shares are not sold at the public offering price, the representatives may change the offering price and the other selling terms.

We and each of our directors and executive officers have agreed with the underwriters not to offer, sell, contract to sell, hedge or otherwise dispose of, directly or indirectly, any of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus continuing through the date 90 days after the date of this prospectus without the prior written consent of UBS Warburg LLC.

In connection with this offering, the underwriters may purchase and sell shares of our common stock in the open market. These transactions may include stabilizing transactions, short sales and purchases to cover positions created by short sales. Stabilizing transactions consist of bids or purchases made for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in this offering. Short sales may be either "covered short sales" or "naked short sales." Covered short sales are sales made in an amount not greater than the underwriters' over-allotment option to purchase additional shares in this offering. The underwriters may close out any covered short position by either exercising their over-allotment option or purchasing

shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned there may be downward pressure on the price of shares in the open market after pricing that could adversely affect investors who purchase in this offering.

The underwriters also may impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

These activities by the underwriters may stabilize, maintain or otherwise affect the market price of our common stock. As a result, the price of our common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued by the underwriters at any time. These transactions may be effected on the Nasdaq National Market or otherwise.

In addition, in connection this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in the common stock on the Nasdaq National Market prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of such transactions. If passive market making is commenced, it may be discontinued at any time.

We have agreed to indemnify the several underwriters against some liabilities, including liabilities under the Securities Act of 1933, and to contribute to payments that the underwriters may be required to make in respect thereof.

An affiliate of Fortis Securities, Inc. has in the past provided financial advisory services to us. For these services we have paid them customary

compensation. In the ordinary course of their respective businesses, the underwriters and certain of their affiliates may in the future engage in investment and commercial banking or other transactions with us, including the provision of certain advisory services and making loans to us.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are a public company and file proxy statements and annual, quarterly and special reports and other information with the SEC. You can inspect and copy the registration statement as well as the reports, proxy statements and other information we have filed with the SEC at the public reference room maintained by the SEC at 450 Fifth Street, N.W., Washington, D.C. 20549, and at the SEC Regional Offices located at Citicorp Center, 500 West Madison Street, Suite 1400, Chicago, Illinois 60661-2511. You can call the SEC at 1-800-732-0330 for further information about the public reference rooms. We are also required to file electronic versions of these documents with the SEC, which may be accessed from the SEC's World Wide Web site at http://www.sec.gov. Reports, proxy and information statements and other information concerning Isis may be inspected at The Nasdaq Stock Market at 1735 K Street, N.W., Washington, D.C. 20006.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" certain of our publicly-filed documents into this prospectus, which means that information included in those documents is considered part of this prospectus. Information that we file with the SEC after the effective date of this prospectus will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until all the shares of common stock that are part of this offering are sold.

The following documents filed with the SEC are incorporated by reference in this prospectus:

1. Our Annual Report on Form 10-K/A for the year ended December 31, 2000.

2. Our Quarterly Report on Form 10-Q for the period ended March 31, 2001 and our Quarterly Report on Form 10-Q, as amended on August 15, 2001, for the period ended June 30, 2001.

3. Our Current Report on Form 8-K, filed with the SEC on August 29, 2001.

4. Our Current Report on Form 8-K/A, filed with the SEC on October 5, 2001.

5. The description of our common stock in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001.

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the termination of the offering of the common stock offered in this prospectus shall be deemed incorporated by reference into this prospectus and to be a part of this prospectus from the respective dates of filing such documents.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, other than exhibits to those documents. You should direct any requests for documents to Vice President of Finance at Isis' principal executive offices at 2292 Faraday Avenue, Carlsbad, California 92008, telephone number (760) 931-9200.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus shall be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus or in any subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus modifies, supersedes or replaces such

statement. Any statement so modified, superseded or replaced shall not be deemed, except as so modified, superseded or replaced, to constitute a part of this prospectus.

LEGAL MATTERS

The validity of the issuance of the common stock offered hereby will be passed upon for us by Cooley Godward LLP, San Diego, California. Dewey Ballantine LLP, New York, New York, is counsel for the underwriters in connection with the offering.

EXPERTS

Ernst & Young LLP, independent auditors, have audited our consolidated financial statements included in our Annual Report on Form 10-K, as amended on April 2, 2001, for the year ended December 31, 2000, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all expenses payable by us in connection with the sale of the 5,750,000 shares of common stock being registered. All the amounts shown are estimates except for the registration fee.

SEC registration fee	$ 25,559
NASD filing fee	10,724
Blue Sky fees and expenses	7,500
Printing and engraving expenses	100,000
Legal fees and expenses	85,000
Accounting fees and expenses	30,000
Miscellaneous	51,217
Total	$310,000

ITEM 15. INDEMNIFICATION OF OFFICERS AND DIRECTORS

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

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

also does not affect a director's responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

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

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

ITEM 16. EXHIBITS

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
*1.1	Form of Underwriting Agreement.
4.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
4.2	Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001. (7)
4.3	Bylaws. (7)
4.4	Certificate of Designation of the Series A Convertible Preferred Stock.(2)
4.5	Certificate of Designation of the Series B Convertible Preferred Stock.(6)
4.6	Certificate of Designation of the Series C Junior Participating Preferred

Stock.(8) 4.7 Specimen Common Stock Certificate. (1) 4.8 Specimen Series A Preferred Stock Certificate. (9) 4.9 Specimen Series B Preferred Stock Certificate. (9) 4.10 Form of Right Certificate. (8) 4.11 Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(3) 4.12 First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(4) 4.15 Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential

	information deleted). (10)
4.16	Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements. (5)
4.17	Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant, together with the related Amendment to the Stock Purchase Agreement. (11)

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
4.18	Subscription, Joint Development and Operating

Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements. (6) 4.19 Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company. (12) 4.20 Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12) 4.21 Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12) 5.1 Opinion of Cooley Godward LLP. 23.1 Consent of Ernst & Young LLP, independent auditors. 23.2 Consent of Cooley Godward LLP. Reference is

made to
Exhibit 5.1.
24.1 Power
of Attorney.
Reference is
made to page
II-5

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* To be filed by amendment.

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 333-39640) or amendments thereto and incorporated herein by reference.

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(12) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 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 pubic 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, a post-effective amendment to this registration statement (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933; (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement; (iii) 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; provided however, that clauses

(i) and (ii) do not apply if the information required to be included in a post-effective amendment by these clauses is contained in periodic reports filed by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the Registration Statement; (2) that, for the purpose of determining any liability under the Securities Act, 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; (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; and (3) for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to 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.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 8th day of October, 2001.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER, DIRECTOR (PRINCIPAL FINANCIAL AND ACCOUNTING 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 this Registration Statement and to sign any Registration Statement that is to be effective on filing pursuant to Rule 462(b) promulgated under the Securities Act of 1933, and all post-effective amendments thereto, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange commission, granting unto said attorneys-in-fact and agents, and each of them, full power of authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, each acting alone, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed below by the following persons in the capacities indicated and on the dates indicated.

NAME	TITLE	DATE
/s/ STANLEY T. CROOKE	Chairman of the Board and Chief Executive Officer -- (Principal executive officer)	October 8, 2001
Stanley T. Crooke, M.D., Ph.D.		
/s/ B. LYNNE PARSHALL	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer), Director	October 8, 2001
B. Lynne Parshall		

/s/ CHRISTOPHER F.O. GABRIELI	Director	October 8, 2001
Christopher F.O. Gabrieli		
/s/ WILLIAM R. MILLER	---	

Director
October 8,
2001
William R.
Miller /s/
FREDERICK
T. MUTO --

- Director
October 8,
2001
Frederick
T. Muto
/s/ MARK
B.
SKALETSKY

Director
October 8,
2001 Mark
B.
Skaletsky
/s/ JOSEPH
H. WENDER

Director
October 8,
2001
Joseph H.
Wender

EXHIBIT INDEX

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
*1.1	Form of Underwriting Agreement.
4.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
4.2	Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001.(7)
4.3	Bylaws. (7)
4.4	Certificate

of Designation of the Series A Convertible Preferred Stock.(2) 4.5 Certificate of Designation of the Series B Convertible Preferred Stock.(6) 4.6 Certificate of Designation of the Series C Junior Participating Preferred Stock.(8) 4.7 Specimen Common Stock Certificate. (1) 4.8 Specimen Series A Preferred Stock Certificate. (9) 4.9 Specimen Series B Preferred Stock Certificate. (9) 4.10 Form of Right Certificate. (8) 4.11 Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(3) 4.12 First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due

November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(4) 4.15 Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (10) 4.16 Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements. (5) 4.17 Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant, together with the

related Amendment to the Stock Purchase Agreement. (11) 4.18 Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements. (6) 4.19 Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12) 4.20 Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12) 4.21 Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12) 5.1 Opinion

of Cooley Godward LLP.

EXHIBIT NUMBER	DESCRIPTION OF DOCUMENT
23.1	Consent of Ernst & Young LLP, independent auditors.
23.2	Consent of Cooley Godward LLP. Reference is made to Exhibit 5.1.
24.1	Power of Attorney. Reference is made to page II-5

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EXHIBIT 5.1

[Cooley Godward Logo]

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425 893-7700
Menlo Park, CA
650 843-5100

Palo Alto, CA
650 843-5000
Reston, VA
703 456-8000

San Francisco, CA
415 693-2000

October 9, 2001

ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested our opinion with respect to certain matters in connection with the filing by ISIS PHARMACEUTICALS, INC., a Delaware corporation (the "Company") of a Registration Statement on Form S-3 (the "Registration Statement") with the Securities and Exchange Commission, covering an underwritten public offering of up to 5,750,000 shares of Common Stock (the "Shares"), including 750,000 shares subject to the Underwriters' over-allotment option.

In connection with this opinion, we have examined and relied upon the Registration Statement and related Prospectus, the Company's Certificate of Incorporation and Bylaws, as amended, and the originals or copies certified to our satisfaction of such records, documents, certificates, memoranda and other instruments as in our judgment are necessary or appropriate to enable us to render the opinion expressed below. We have assumed the genuineness and authenticity of all documents submitted to us as originals, the conformity to originals of all documents submitted to us as copies thereof and the due execution and delivery of all documents where due execution and delivery are a prerequisite to the effectiveness thereof.

On the basis of the foregoing, and in reliance thereon, we are of the opinion that the Shares, when issued and sold in accordance with the Registration Statement and related Prospectus, will be validly issued, fully paid and nonassessable.

We consent to the reference to our firm 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,

Cooley Godward LLP

By: ____/s/ Julie M. Robinson____
Julie M. Robinson

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG, INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of 5,750,000 shares of its common stock and to the incorporation by reference therein of our report dated February 2, 2001, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K, as amended on April 2, 2001) for the year ended December 31, 2000, to be filed with the Securities and Exchange Commission on or about October 9, 2001.

/s/ Ernst & Young LLP_____
ERNST & YOUNG LLP

San Diego, California
October 8, 2001