PROSPECTUS

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 22, 2001, the last reported sales price of our common stock on the Nasdaq National Market was $20.15 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	$20.00	$100,000,000
Underwriting discount and commissions	$ 1.20	$ 6,000,000
Proceeds, before expenses, to us	$18.80	$ 94,000,000

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 October 25, 2001.

UBS Warburg

Robertson Stephens

Needham & Company, Inc.

Fortis Securities Inc.

The date of this prospectus is October 22, 2001

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 a price of $20.00 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.

Nine Months ended September 30,	Years Ended December 31,					
	2000	1999	1998	1997	1996	
Statement of operations data (unaudited)						
	(in thousands, except per share amounts)					
Total revenues	$37,255	$33,925	$39,171	$32,722	$22,663	
Research and development expenses	57,014	66,413	62,200	55,940	45,653	
Net loss applicable to common stock	(54,699)	(59,645)	(42,983)	(31,066)	(26,521)	
Basic and diluted net loss per share	(1.48)	(2.08)	(1.60)	(1.17)	(1.04)	
Shares used in computing basic and diluted net loss per share	37,023	28,703	26,873	26,456	25,585	

As of September 30, 2001		
	Actual	As Adjusted(1)
Balance sheet data		
	(in thousands, unaudited)	
Cash, cash equivalents and short-term investments	$213,202	$306,892
Working capital	183,852	277,542
Total assets	294,412	388,102
Long-term debt and capital lease obligations, less current portion	123,651	123,651
Accumulated deficit	(370,635)	(370,635)
Stockholders'		

equity.....	118,030
	211,720

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(1) THE FINANCIAL DATA ABOVE EXCLUDES TRANSACTIONS SUBSEQUENT TO SEPTEMBER 30, 2001, INCLUDING $5 MILLION RECEIVED FROM LILLY ON OCTOBER 18, 2001 RELATED TO THE $100 MILLION LOAN LILLY COMMITTED TO LEND ISIS.

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 September 30, 2001, our accumulated losses were approximately $371 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 U.S. 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 October 22, 2001, the market price of our common stock has ranged from $7.88 to $21.98 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 chief executive officer. 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 $16.80 per share in the net tangible book value per share of our common stock, at the public offering price of $20.00 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 September 30, 2001, would have been $3.20 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 $93.7 million at the public offering price of $20.00 per share. If the underwriters exercise the over-allotment option in full, the net proceeds to us will be approximately $107.8 million. "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 September 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, at the public offering price of $20.00 per share and after deducting underwriting discounts and commissions and estimated offering expenses to be paid by us:

	As of September 30, 2001	
	Actual	As Adjusted(1)
	(in thousands, except share data)	
Cash, cash equivalents and short term investments	$ 213,202	$ 306,892
Long-term debt and capital lease obligations, less current portion	$ 123,651	$ 123,651
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	1,542	1,542
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	1,060	1,060
Common stock, $.001 par value; 100,000,000 shares authorized, 47,087,796 shares issued and outstanding, actual; and 52,087,796 shares issued and outstanding, as adjusted	47	52
Additional paid-in capital	461,267	554,952
Deferred compensation	(297)	(297)
Accumulated other comprehensive income	1,016	1,016
Accumulated deficit	(370,635)	(370,635)
Total stockholders' equity	118,030	211,720
Total capitalization	$ 241,681	$ 335,371

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(1) THE FINANCIAL DATA ABOVE EXCLUDES TRANSACTIONS SUBSEQUENT TO SEPTEMBER 30, 2001, INCLUDING $5 MILLION RECEIVED FROM LILLY ON OCTOBER 18, 2001 RELATED TO THE $100 MILLION LOAN LILLY COMMITTED TO LEND ISIS.

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

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 22, 2001)	21.98	16.70

On October 22, 2001, the last reported sale price for our common stock was $20.15 per share, and there were approximately 1,044 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.

Dilution

Our net tangible book value as of September 30, 2001 was $72,897,000, or approximately $1.55 per share of common stock. Net tangible book value per share represents the amount of our tangible assets less total liabilities, divided by 47,087,796 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 a public offering price of $20.00 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 September 30, 2001 would have been $166,587,000, or $3.20 per share, an immediate increase of $1.65 per share over the net tangible book value to existing stockholders and an immediate dilution of $16.80 per share to the adjusted net tangible book value to purchasers of common stock in this offering, as illustrated in the following table:

Public offering price per share		$20.00
Net tangible book value per share at September 30, 2001	$1.55	
Increase per share attributable to new investors in this offering	1.65	
Pro forma adjusted net tangible book value per share after offering		$ 3.20

Net tangible book value dilution per share to new investors in this offering	$16.80

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.

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 nine-month periods ended September 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 nine months ended September 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.

	Years Ended December 31,				Nine Months ended September 30,	
	2000	1999	1998	1997	1996	2001	2000
Statement of operations data: (unaudited)							
	(in thousands, except per share data)						
Total revenues	$37,255	$33,925	$39,171	$32,722	$22,663	$ 31,529	$29,319
Research and development expenses	57,014	66,413	62,200	55,940	45,653	58,954	41,986
Net loss applicable to common stock	(54,699)	(59,645)	(42,983)	(31,066)	(26,521)	(59,175)	(38,936)
Basic and diluted net loss per share	(1.48)	(2.08)	(1.60)	(1.17)	(1.04)	(1.43)	(1.08)
Shares used in computing basic and diluted net loss per share	37,023	28,703	26,873	26,456	25,585	41,517	36,172

	As of December 31,					As of September 30,
	2000	1999	1998	1997	1996	2001
Balance sheet data: (unaudited)						
	(in thousands)					
Cash, cash equivalents and short-term investments	$127,262	$ 52,839	$ 58,848	$ 86,786	$ 77,624	$ 213,202
Working capital	118,568	44,213	40,651	62,573	56,300	183,852
Total assets	183,256	103,107	96,074	117,881	101,305	294,412
Long-term debt and capital lease obligations, less current portion	102,254	87,254	77,724	56,452		

19,864 123,651 Accumulated deficit.....
(311,460) (256,761) (197,116)
(154,133) (123,067) (370,635)
Stockholders' equity (deficit)..... 66,366 869
(4,186) 34,852 58,385 118,030

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	2,282,500
Robertson Stephens, Inc.	1,186,900
Needham & Company, Inc.	867,350
Fortis Securities Inc.	228,250
Lazard Freres & Co. LLC	75,000
Morgan Stanley & Co. Incorporated	75,000
SG Cowen Securities Corporation	75,000
Dominick & Dominick LLC	35,000
Wells Fargo Van Kasper	35,000
Gruntal & Co. L.L.C.	35,000
Loeb Partners Corporation	35,000
Moors & Cabot, Inc.	35,000
Roth Capital Partners LLC	35,000
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 of over-allotment option	Full Exercise of over-allotment option
Per share	$ 1.20	$ 1.20
Total	$6,000,000	$6,900,000

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 $0.72 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 $0.10 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.

Fortis Bank (Nederland) N.V., an affiliate of Fortis Securities Inc., a co-managing underwriter of this offering, received $60,000 in advisory fees from the Company in the six month period preceding the October 9, 2001 filing of the Registration Statement for this offering. These fees are deemed underwriting compensation under the NASD's Conduct Rules. 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:

- our Annual Report on Form 10-K/A for the year ended December 31, 2000;

- our Quarterly Report on Form 10-Q for the period ended March 31, 2001;

- our Quarterly Report on Form 10-Q, as amended on August 15, 2001, and on October 11, 2001, for the period ended June 30, 2001;

- our Quarterly Report on Form 10-Q for the period ended September 30, 2001;

- our Current Report on Form 8-K, filed with the SEC on August 29, 2001;

- our Current Report on Form 8-K/A, filed with the SEC on October 5, 2001; and

- 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.

[LOGO]