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Registration No. 333-89626

PROSPECTUS

2,820,214 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

We are registering our common stock for resale by the selling stockholders identified in this prospectus. We are not selling any shares of our common stock under this prospectus and will not receive any of the proceeds from the sale of shares by the selling stockholders. Specifically, this prospectus relates to the resale of:

- 423,711 shares of our common stock that were issued to the selling stockholders in connection with our HepaSense Ltd. joint venture;
- up to 750,337 shares of our common stock issuable upon the conversion of shares of our Series A Convertible Preferred Stock held by the selling stockholders;
- 236,185 shares of our common stock issuable upon the exercise of warrants held by the selling stockholders; and
- up to 1,409,981 shares of our common stock issuable upon the conversion of a convertible promissory note held by the selling stockholders.

For a description of the plan of distribution of the resale shares, see page 12 of this prospectus.

Our common stock is currently traded on the Nasdaq National Market under the symbol "ISIS." On June 12, 2002, the last reported sales price for our common stock was $7.50 per share.

Investing in our common stock involves risks.
See "Risk Factors" beginning on page 3.

Neither the securities and exchange commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this Prospectus is June 12, 2002

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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 securities 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.

Our Business

We are a biopharmaceutical company pioneering RNA-based drug discovery technologies to identify and commercialize novel drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information that it needs to produce proteins, including those proteins that are involved in disease. Interference with RNA can keep the body from producing proteins that are involved in disease. We have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors designed to bind with high specificity to their RNA target and modulate protein production. With our Ibis technology, we use our expertise in RNA to design small molecule therapeutics that bind to RNA. We also use our antisense technology in collaborations with pharmaceutical companies 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 drugs.

We used our antisense technology to commercialize our first product, Vitravene. Vitravene demonstrates our ability to meet U.S. Food and Drug Administration, or FDA, regulatory requirements and to manufacture commercial antisense drugs. We have 13 products in our development pipeline with eight in human clinical trials designed to assess safety and efficacy. Our products in development address numerous therapeutic areas with major market potential, including cancer and inflammatory, viral, metabolic and dermatological diseases. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. Our second-generation drugs, which represent approximately half of our drugs in development, may be able to be dosed as infrequently as once per month. We are also making progress on oral formulations for our second-generation drugs.

Affinitac, formerly known as LY900003 or ISIS 3521, is our most advanced product in development. In August 2001, we licensed Affinitac to Eli Lilly and Company as part of a broad strategic collaboration. Affinitac is undergoing Phase III clinical trials in combination with traditional cancer chemotherapy drugs to treat non-small cell lung cancer, the most common form of lung cancer. In January 2002, we completed enrollment of a 600 patient Phase III trial that we initiated in late 2000. We initiated this trial based on promising results in a Phase II trial in patients with non-small cell lung cancer. Results from the Phase II 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 April 2002, Lilly launched a global Phase III trial of Affinitac in patients with non-small cell lung cancer. If the data from our Phase III trial are sufficiently positive to support a single study New Drug Application, or NDA, we and Lilly plan to file the NDA in 2003. If two Phase III studies are required, we and Lilly plan to file the NDA in 2004. In November 2000, the FDA granted Affinitac fast track review status. In November 2001, we initiated a Phase III clinical trial for another product, ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. We have six 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 are collaborating with nine major pharmaceutical partners for these services, which are Abbott Laboratories, Inc.; Amgen Inc.; Aventis (Rhone-Poulenc Rorer); Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; Johnson & Johnson Pharmaceutical Research & Development, LLC; Merck & Co., Inc.; and Pharmacia Corporation. We supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product. This database will 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 that bind to RNA. Beyond its therapeutic focus, Ibis has expanded the application of its technology to develop a new diagnostic platform to detect infectious agents. 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 October 2001, Ibis received a two-year contract from the Defense Advanced Research Projects Agency, or DARPA, to develop a device to detect infectious agents used in biological warfare attacks. Under this two-year contract, for the research program Triangulation Identification Genetic Evaluation of biological Risks, or TIGER, we expect to receive up to $8.9 million in funding. In June 2000, Ibis initiated its first collaboration with a pharmaceutical industry partner, Agouron Pharmaceuticals, Inc., a Pfizer company. In May and October 2001, we received a $2.5 million milestone payment and a $1.5 million milestone payment, respectively, under this collaboration. This collaboration is scheduled to end in June 2002 in accordance with its terms.

We have a broad patent portfolio relating to our technologies. We have rights to more than 900 issued patents, which we believe represent the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. In 2001, we continued to fortify our antisense technology portfolio by exclusively licensing Hybridon's antisense chemistry and delivery technology patents. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. The principal purpose of our intellectual property portfolio is to protect our inventions in RNA-based drug discovery. Our intellectual property estate also enables us to expand our pipeline by granting partners limited access to antisense technology. Licensing partnerships may include antisense and Ibis drug discovery alliances such as those we have with Lilly and Amgen, GeneTrove functional genomics collaborations such as those we have with Chiron, Amgen and Pharmacia or licenses to non-antisense patents for drug discovery such as our license to Eyetech Pharmaceuticals, Inc.

Isis was incorporated in California in January 1989 and in April 1991 changed its state of incorporation to Delaware. Our executive offices are located at 2292 Faraday Avenue, Carlsbad, California 92008, and our telephone number is (760) 931-9200.

Isis Pharmaceuticals™, GeneTrove™ and Ibis Therapeutics™ are our trademarks. Vitravene® is a registered trademark of Novartis AG. Affinitac™ is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

RISK FACTORS

Investing in our securities 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 securities. 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 securities could decline, and you might lose all or part of your investment.

RISKS RELATED TO OUR BUSINESS

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, will 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 meeting this goal. 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 cytomegalovirus, or

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. These collaborations may not continue 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, Affinitac, 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 Antisense Therapeutics

Limited, Elan Corporation, plc, Merck & Co., Inc. and OncoGenex Technologies Inc. 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 use 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.

In addition, if 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 March 31, 2002, our accumulated losses were approximately $405 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, cash equivalents and short-term investments at March 31, 2002 combined with investment income, committed contractual cash payments and proceeds from our May 2002 convertible debt offering, will be sufficient to meet our anticipated requirements for at least the next 36 months. 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 by others 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, as well as the price of our other securities, 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 successfully commercialize 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. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products 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 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 provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may 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 patent infringement. On December 12, 2001, we initiated a second action against Sequitur, Inc. alleging patent infringement. On May 2, 2002 we initiated a third action against Sequitur, Inc. alleging patent infringement. If we do not prevail in the defense of these patents, 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 United States 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, the price of our securities 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. 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 the price of our securities 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.

If the price of our securities continues 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. These fluctuations in our common stock price may significantly affect the trading price of the convertible notes. During the 12 months preceding May 1, 2002, the market price of our common stock has ranged from $7.88 to $27.15 per share. The market price of our securities 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, 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 the price of our securities 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 4,166,667 shares of our common stock which are currently outstanding, an additional $4.5 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 the price of our securities.

If the private placement of our $5^{1}/_{2}$% convertible subordinated notes violated securities laws, purchasers in the private placement would have the right to seek refunds or damages.

On May 1, 2002, we issued and sold $125,000,000 of $5^{1}/_{2}$% convertible subordinated notes due 2009 in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the

Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of the securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in the private offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

SPECIAL NOTE 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 services 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" in this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

USE OF PROCEEDS

We will receive no proceeds from this offering. The selling stockholders will receive the proceeds from this offering.

SELLING STOCKHOLDERS

We are registering for resale shares of our common stock held by stockholders litsted below, the selling stockholders. The selling stockholders acquired the resale shares in connection with our Hepasense and Orasense joint ventures with the selling stockholders.

The following table is based in part upon information provided by the selling stockholders and sets forth (i) the name of the selling stockholders; (ii) the number of shares of our common stock that the selling stockholders owned prior to the offering for resale of any of the shares of our common stock being registered hereby; (iii) the maximum number of shares of our common stock that may be offered for resale for the account of the selling stockholders pursuant to this prospectus; and (iv) the percentage of shares of our common stock to be held by the selling stockholders after the offering of the resale shares (assuming all of the resale shares are sold by the selling stockholders). However, our registration of the common stock does not necessarily mean that the selling stockholders will sell all or any of its shares. In addition, the selling stockholders may have sold, transferred or otherwise disposed of, or may sell, transfer or otherwise dispose of, at any time or from time to time since the date on which the selling stockholders provided the information regarding the shares of common stock owned by it, all or a portion of the shares of common stock owned by it in transactions exempt from the registration requirements of the Securities Act of 1933.

The percentage in the table below is based on 54,165,099 shares outstanding on April 30, 2002.

Selling stockholders	Shares Of Common Stock Owned Prior to the Offering	Shares Of Common Stock Offered	Percentage Of Common Stock Outstanding After The Offering
Elan International Services, Ltd.	1,387,646(1)	974,751	*
Elan Pharmaceutical Investments, Ltd.	215,000(2)	215,000	—
Elan Pharmaceutical Investments II, Ltd.	880,126(3)	880,126	—
Elan Pharmaceutical Investments III, Ltd.	750,337(4)	750,337	—

* Less than one percent

(1) Includes 126,092 shares of common stock, 412,895 shares of common stock issuable upon conversion of an outstanding convertible note as of May 31, 2002, and 6,304 shares of common stock issuable upon exercise of outstanding warrants. Also includes 842,255 shares of our common stock issuable upon conversion of a convertible note, assuming a conversion date of April 19, 2005. Elan International Services, Ltd. is a wholly-owned indirect subsidiary of Elan Corporation, plc.

(2) Includes 215,000 shares of common stock issuable upon the exercise of an outstanding warrant. Elan Pharmaceutical Investments, Ltd. is a wholly-owned indirect subsidiary of Elan Corporation, plc.

(3) Includes 297,619 shares of common stock, 567,626 shares of common stock issuable upon conversion of an outstanding convertible note, assuming a conversion date of April 19, 2005, and 14,881 shares of common stock issuable upon exercise of an outstanding warrant. Elan Pharmaceutical Investments II, Ltd. is a special purpose entity established by Elan International Services, Ltd. under SFAS 125 and a wholly-owned indirect subsidiary of Elan Corporation, plc.

(4) Includes 750,337 shares of common stock issuable upon conversion of the shares of our Series A Convertible Preferred Stock, assuming a conversion date of April 20, 2005. Elan Pharmaceutical

Investments III, Ltd. is a special purpose entity established by Elan International Services, Ltd. under SFAS 125 and a wholly-owned indirect subsidiary of Elan Corporation, plc.

In April 1999, we formed a joint venture with Elan, called Orasense, to develop a platform technology for the oral delivery of antisense drugs. As part of the transaction, Elan purchased 910,844 shares of our common stock. In December 2001, Elan sold these shares of common stock. Elan also purchased shares of our Series A preferred stock which is convertible into either our stock or stock in Orasense. As part of the transaction, we also issued warrants to purchase 215,000 shares of our common stock to Elan, at an exercise price of $24.00 per share. As part of the agreement, Elan made available to us an $18.4 million line of credit that we may use to provide funding to Orasense, subject to Elan's agreement. Assuming a conversion date of April 19, 2005, this note is convertible into 1,409,981 shares of our common stock, at a weighted average conversion price of $18.35 per share.

In January 2000, we formed a joint venture with Elan, called HepaSense, to develop an antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus or HCV. As part of the transaction, Elan purchased 297,619 shares of our common stock for an aggregate purchase price of $7.5 million. Elan also purchased shares of our Series B preferred stock which is convertible in the future into either our stock or stock in HepaSense. As part of the transaction, we also issued warrants to purchase 14,881 shares of our common stock to Elan at an exercise price of $50.40 per share. In addition, Elan made available to us a $12.0 million line of credit that we may use to provide funding to HepaSense, subject to Elan's agreement. As of May 31, 2002, this note was convertible into 412,895 shares of our common stock, at a weighted average conversion price of $19.77 per share.

In April 2002, Elan purchased 126,092 shares of our common stock for an aggregate purchase price of $3.75 million and a warrant to purchase 6,304 shares of our common stock at an exercise price of $59.48 per share in connection with the achievement of a milestone under the HepaSense joint venture. Elan may purchase an additional $3.75 million of our common stock upon completion of a mutually agreed milestone.

PLAN OF DISTRIBUTION

The selling stockholders may sell the resale shares from time to time in one or more transactions at:

- fixed prices;
- market prices at the time of sale;
-

varying prices determined at the time of sale; or

- negotiated prices.

The selling stockholders will act independently of us in making decisions regarding the timing, manner and size of each sale. In addition, a selling shareholder's donees, pledgees, transferees and other successors in interest may sell shares received from a named selling shareholder after the date of this prospectus. In that case, the term "selling shareholders" as used in this prospectus includes such donees, pledgees, transferees and other successors in interest. The selling stockholders may effect these transactions by selling the resale shares to or through broker-dealers. Broker-dealers engaged by the selling stockholders may arrange for other broker-dealers to participate in the resales. The shares may be sold by way of any legally available means, including in one or more of the following transactions:

- a block trade in which a broker-dealer attempts to sell the shares as agent but may resell a portion of the block as principal to facilitate the transaction;
- a purchase by a broker-dealer as principal and resale by the broker-dealer for its account under this prospectus;
- an exchange distribution in accordance with the rules of the exchange;
- ordinary brokerage transactions and transactions in which a broker solicits purchasers;
- on any national securities exchange or quotation service at which the common stock may be listed or quoted at the time of sale including the NASDAQ National Market;
- in the over-the-counter market;
- through options;
- by pledge to secure debts and other obligations;
- privately negotiated transactions; and
- a combination of any of the above transactions.

If required, we will distribute a supplement to this prospectus to describe material changes in the terms of the offering.

Broker-dealers or agents may receive compensation from the selling stockholders in the form of commissions, discounts or concessions. Broker-dealers or agents may also receive compensation from the purchasers of the resale shares for whom they act as agents or to whom they sell as principals, or both. A broker-dealer's compensation will be negotiated in connection with the sale and may exceed the broker-dealer's customary commissions. Broker-dealers, agents or the selling stockholders may be deemed to be "underwriters" within the meaning of the Securities Act in connection with sales of the resale shares. Any commission, discount or concession received by these broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting discounts or commissions under the Securities Act.

Because the selling stockholders may be deemed to be an "underwriter" within the meaning of the Securities Act, they will be subject to the prospectus delivery requirements of the Securities Act. In

addition, any securities covered by this prospectus which qualify for sale pursuant to Rule 144 under the Securities Act may be sold under Rule 144 rather than under this prospectus.

Under applicable rules and regulations under the Exchange Act, any person engaged in the distribution of the resale shares may not simultaneously engage in market making activities with respect to our common stock for a period of two business days prior to the commencement of the distribution.

In addition, the selling stockholders will be subject to applicable provisions of the Exchange Act and the rules and regulations thereunder, including Regulation M, which may limit the timing of purchases and sales of shares of our common stock by the selling stockholders or any other person. We will make copies of this prospectus available to the selling stockholders and have informed them of the need to deliver a copy of this prospectus to each purchaser at or prior to the time of the sale.

We will pay all costs, expenses and fees associated with the registration of the resale shares, estimated to be $25,000. The selling stockholders will pay all commissions and discounts, if any, associated with the sale of the resale shares. The selling stockholders may agree to indemnify any broker-dealer or agent that participates in sales of the resale shares against specified liabilities, including liabilities arising under the Securities Act. The selling stockholders have agreed to indemnify certain persons, including broker-dealers and agents, against specified liabilities in connection with the offering of the resale shares, including liabilities arising under the Securities Act.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of

- Series A Convertible Exchangeable 5% Preferred Stock, 120,150 shares of which were authorized, issued and outstanding at March 31, 2002;
- Series B Convertible Exchangeable 5% Preferred Stock, 16,620 shares of which were authorized and 12,015 shares of which were issued and outstanding at March 31, 2002;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at March 31, 2002; and
- Common stock, 100,000,000 shares of which are authorized and 53,974,109 shares of which were outstanding as of March 31, 2002.

The description of our common stock is incorporated by reference to filings with the SEC. See "Incorporation by Reference."

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain any future earnings to support operations and to finance the growth and development of our business and we do not anticipate paying cash dividends for the foreseeable future.

LEGAL MATTERS

The validity of the issuance of the common stock offered hereby will be passed upon for us by Grantland E. Bryce our Vice President, Legal and General Counsel.

EXPERTS

Ernst & Young LLP, independent auditors, have audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2001, 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 upon their authority as experts in accounting and auditing.

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 175 West Jackson Blvd., Ste. 900, Chicago, Illinois 60604 and 233 Broadway, New York, New York 10279. You can call the SEC at1-800-732-0330 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.

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 for the year ended December 31, 2001;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2002;
- our Current Report on Form 8-K, filed with the SEC on January 4, 2002;
- our Current Report on Form 8-K, filed with the SEC on January 7, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 23, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 24, 2002;
- our Current Report on Form 8-K, filed with the SEC on April 24, 2002; 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.

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.

You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus or any prospectus supplement. This prospectus is not an offer of these securities in any jurisdiction where an offer and sale is not permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock.

2,820,214 Shares
Common Stock

ISIS PHARMACEUTICALS, INC.

Prospectus

June 12, 2002

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