QuickLinks -- Click here to rapidly navigate through this document

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2003

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For The Transition Period From to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

2292 Faraday Ave., Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☒ No o

The approximate aggregate market value of the voting common stock held by non-affiliates of the registrant, based upon the last sale price of the common stock reported on the National Association of Securities Dealers Automated Quotation National Market System was $227,642,048 as of June 30, 2003.*

The number of shares of voting common stock outstanding as of March 3, 2004 was 55,883,687.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Portions of the registrant's definitive Proxy Statement filed on or about April 15, 2004 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 26, 2004, is incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 59 to 63 incorporates several documents by reference as indicated therein.

* Excludes 12,762,386 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 2003. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

This Form 10-K contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and systems used to identify infectious agents, discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Form 10-K. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this Form 10-K including those identified in the section of Item 1 entitled "Risk Factors". As a result, you should not rely on these forward-looking statements.

Vitravene® is a registered trademark of Novartis AG. Taxotere® is a registered trademark of Aventis Pharmaceuticals, Inc. GeneTrove® and Ibis Therapeutics® are registered trademarks of Isis Pharmaceuticals, Inc. Affinitak™ is a trademark of Eli Lilly and Company. HepaSense™ is a trademark of HepaSense Ltd. Orasense™ is a trademark of Orasense Ltd. Macugen™ is a trademark of Eyetech Pharmaceuticals, Inc. Alnylam® is a registered trademark of Alnylam Pharmaceuticals, Inc. InterfeRx™ is a trademark of Alnylam Pharmaceuticals, Inc.

PART I

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company exploiting proprietary 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 the cell needs to produce proteins, including those proteins 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, or oligonucleotides, designed to hybridize, or bind, with high specificity to their RNA target and modulate the production of proteins associated with diseases. We also use our antisense technology in collaborations with pharmaceutical companies to identify and prioritize attractive gene targets for their drug discovery programs. We are a leader in exploiting RNA as a target for drugs. Within our Ibis program, we are expanding on our RNA expertise by creating a platform technology designed to rapidly and accurately identify a broad range of organisms in a single test. Our ongoing development of this technology and a biosensor system related to this technology have been funded primarily by agencies of the United States Government.

We used our antisense technology to commercialize our first product, Vitravene®. Vitravene demonstrates our ability to meet Food and Drug Administration, or FDA, and European regulatory requirements and to commercially manufacture antisense drugs. We currently have 11 antisense products in our development pipeline with 10 in human clinical trials designed to assess safety and efficacy. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, viral, metabolic, dermatological, and cardiovascular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. In addition, we are advancing antisense drugs using second-generation chemistry. Physicians may be able to dose our second-generation drugs, which represent over half of our drugs in development, as infrequently as once per month. We are also making progress on developing oral formulations of our second-generation drugs. Recent clinical trial data showed the potential feasibility of oral solid dosage forms for antisense drugs. This oral formulation platform may increase the commercial competitiveness of any antisense drugs we may develop and broaden their applicability.

Affinitak™, formerly LY900003 or ISIS 3521, which we licensed to Eli Lilly and Company, or Lilly, in 2001, is our most advanced product in development. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single study new drug application. Lilly and we completed an analysis of the data from this trial and presented a summary of the findings at the 39th Annual Meeting of the American Society of Clinical Oncology in June 2003. In a second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which most likely will occur in the second half of 2004.

We are conducting two Phase III clinical trials for another product, ISIS 2302, or alicaforsen, in an inflammatory bowel disease known as Crohn's disease. We are conducting these trials in North America and Europe. We expect to report data from these clinical trials in the second half of 2004. We also have Phase II programs ongoing for five additional products.

Our GeneTrove® program uses our antisense technology as a tool to provide important information about the function of genes and has automated the initial steps in our antisense drug

discovery process. Our current focus is to use GeneTrove information to direct our own drug discovery research and that of our antisense drug discovery partners, like Lilly and Amgen.

Within our Ibis program we have invented a platform technology that has the potential to revolutionize the identification of organisms that cause infectious diseases. Through a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we have applied our proprietary technologies to develop a biological sensor, or biosensor, designed to rapidly and simultaneously identify a broad range of infectious organisms in a sample, including organisms

that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. To date, we have received grants and contracts representing potential funding of up to $55 million from agencies of the U.S. Government, including the Defense Advanced Research Projects Agency, or DARPA, the Centers for Disease Control and Prevention, or CDC, the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, the United States Navy, and the Federal Bureau of Investigation, or FBI, among others.

We have a broad patent portfolio covering our technologies. We have rights to more than 1,300 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 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 through licenses we grant them. Licensing partnerships may include antisense drug discovery collaborations such as those we have with Lilly and Amgen, as well as GeneTrove functional genomics agreements like those we have with Amgen, Chiron and Pharmacia. In addition, we have licensed our functional genomics patents to companies like Chiron, Amgen, Sequitur and atugen AG. We also license our non-antisense patents, as we did to Eyetech Pharmaceuticals, Inc, or Eyetech. In December 2001, we licensed several chemistry patents to Eyetech for the development of Macugen™, a drug designed to treat age-related macular degeneration, or AMD, that Eyetech is co-developing with Pfizer. In 2003, Pfizer and Eyetech reported encouraging Phase III data for Macugen that Eyetech says will serve as the basis for a new drug application, or NDA, with commercialization of the drug expected in 2005. Assuming successful commercialization of Macugen, we have the opportunity to earn future milestone payments and royalties that could be substantial to us. To date, we have generated more than $35 million in license and royalty fees related to our patent portfolio.

We incorporated in California in 1989, and in 1991 we reincorporated as a Delaware corporation. Our principal offices are in Carlsbad, California. In November 2003, we established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary in Singapore.

Drug Discovery and Development

From our progress in antisense we have developed a robust pipeline of promising new drugs and efficient genomics tools that unlock value from gene sequence data. Our Ibis program has the potential to become an important new approach to the identification and treatment of infectious diseases.

Antisense Technology Platform

Antisense Drug Discovery

Proteins are essential, working molecules in a cell. Almost all human diseases result from inappropriate protein production or improper protein activity. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense technology is different from traditional drug discovery because it specifically targets

disease-causing proteins before the body produces them. We design our antisense drugs, or antisense inhibitors, to act earlier in the disease process than traditional drugs and to interrupt the production of disease causing proteins without disrupting proteins responsible for the body's normal functioning.

Genes contain the information necessary to produce proteins. A gene is made up of bases, or nucleotides: Adenine, Thymine, Guanine, and Cytosine, commonly known as A, T, G and C, which are linked together to form a two-stranded structure that resembles a twisted ladder, known as DNA or deoxyribonucleic acid. The nucleotides on one side of the ladder bind weakly to complementary nucleotides on the other strand according to specific rules; for example, A pairs with T and G pairs with C, creating the ladder's rungs. This highly specific nucleotide pairing is called hybridization. The sequence or order of these nucleotides establishes the cell's recipe for making proteins.

When a cell transcribes information from DNA into messenger RNA, or mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template and information stored in the DNA strand is copied into a complementary mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in so doing, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the production of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the "sense" strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand.

We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides, which resemble DNA and RNA and are the complement of mRNA. These potent antisense oligonucleotides, or antisense drugs, inhibit the production of disease-causing proteins. Antisense drugs can selectively inhibit one protein among a closely related group of proteins because antisense drugs interact selectively with the specific RNA and not with RNA of the closely related members of the group. It is easier to differentiate between closely related proteins at the RNA sequence level than by binding to the protein itself, as traditional drugs do. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique specificity means that antisense drugs may be far less toxic than traditional drugs, because we can design them to minimize the impact on unintended targets.

Further, the design of antisense compounds is less complex, more rapid and more efficient than traditional drug design directed at protein targets. Traditional drug design requires companies to identify a small molecule that will interact with protein structures to affect the disease-causing process. Since predicting which small molecules will do this has proven to be difficult, traditional drug discovery involves testing hundreds of thousands of small molecules for their ability to interfere with protein function. As a result, traditional drug discovery is a labor intensive, low probability endeavor. In contrast, we design our antisense compounds to bind to mRNA structures through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the mRNA receptor.

We are the leader in the discovery and development of this exciting new class of therapeutic compounds. Our proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drug candidates for optimal use with particular targets and thus to produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, over the past decade, our scientists have made great advancements in chemistries, which we call our second-generation antisense drugs. Second-generation drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. We have also made significant progress in developing new formulations of antisense drugs, like oral, topical cream,

subcutaneous, intravitreal, aerosol and enema, of antisense drugs that further expand the potential for antisense technology.

In our functional genomics program, GeneTrove, we use antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. This information forms the basis of the first step of our antisense drug discovery program. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. We have created inhibitors to thousands of genes, validated many targets and dissected numerous disease pathways. Additionally, we have created libraries of antisense inhibitors to identify novel gene function. Our GeneTrove program has enhanced our own antisense drug discovery efforts and our patent portfolio through custom target validation collaborations and intellectual property licenses while generating near-term revenue for us.

Ibis Technology Platform

Through our Ibis program, we have expanded on our RNA-based drug discovery and development expertise to create a platform technology designed to rapidly and accurately identify a broad range of organisms in a single test, and to develop small molecule antibacterial and antiviral drugs that bind to RNA. To accomplish these tasks, our scientists integrate functional genomics, bioinformatics and RNA-focused chemistry programs with novel high-throughput, mass spectrometry-based screening methods.

We are collaborating with San Diego-based Science Applications International Corporation, or SAIC, on a multi-year project funded by DARPA for the ongoing development of our TIGER technology and biosensor. This project combines our expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal processing capabilities. As of December 31, 2003, we had been awarded funding of $13.3 million related to this collaboration with SAIC, of which $13.3 million had been billed and $11.9 million had been collected. During 2003, we successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. In March 2004, we were awarded a two-year contract under this collaboration for additional funding of up to $19.5 million to further the ongoing development of TIGER, including the design and manufacture of a fully integrated, self-contained system, called TIGER 2.0. We are designing this instrument to perform the analysis of samples in an automated manner, and expect to initially deploy it for use by our government partners, including the CDC.

In September 2003, we received a three-year grant for up to $6.0 million from the CDC to develop and apply our TIGER technology to the surveillance of human infectious disease in the U.S. Using the grant from the CDC, we expect to develop and provide TIGER technology for CDC projects focused on emerging human infectious diseases. We believe our work to automate the TIGER biosensor and deploy the system for specific applications for the CDC and DARPA advances our TIGER technology toward commercialization. We retain full commercial rights to the TIGER technology while our government partners have access to the technology to meet their specific needs.

Since Ibis' inception, we have received significant financial support from government-funded grants and contracts to use Ibis' technology to assist in national defense. In March 2002, we transitioned our government-sponsored research program to discover novel broad-spectrum antibacterial drugs for biological warfare defense to USAMRIID. USAMRIID awarded us a three-year, $2.4 million contract to advance our work in this area.

In addition to DARPA, USAMRIID and the CDC, we also have research relationships with other government entities including the United States Navy and the FBI. To date, we have received government contracts and grants representing potential funding of up to $55 million. During 2003,

revenue generated from agencies of the U.S. Government comprised 20% of our total revenue, including approximately 16% of our total revenue from our collaboration with SAIC.

Approved Product and Products Under Development

We have successfully developed the first antisense drug to reach the market, Vitravene, for CMV retinitis, which is available through our partner, Novartis Opthalmics AG.

We have designed our drugs in development to treat a variety of health conditions, including inflammatory, viral, metabolic, cardiovascular and dermatological diseases, and cancer, and we are studying them in intravenous, subcutaneous, topical cream, enema and oral formulations. Intravenous and subcutaneous formulations are commonly grouped together and referred to as parenteral forms of administration. The following table lists our approved product and each of our products under development, its target, disease indication and development status, as well as our commercial rights.

Approved Product and Products Under Development

Product(1)	Target	Potential Disease Indication(s)	Development Status(2)	Commercial Rights
Vitravene (I)	Antiviral	CMV Retinitis	Available in the U.S..	Isis/Novartis Ophthalmics AG(3)
Affinitak™ (formerly LY900003 or ISIS 3521) (P)	PKC-alpha	Cancer—Non-Small Cell Lung Cancer	Phase III	Lilly
Alicaforsen (ISIS 2302) (P)	ICAM-1	Crohn's Disease	Phase III	Isis
Alicaforsen (ISIS 2302) (E)	ICAM-1	Ulcerative Colitis, Pouchitis	Phase II	Isis
ISIS 14803 (P)	Hepatitis C virus	Hepatitis C	Phase II	Isis
ISIS 104838 (P,O)*	TNF-alpha	Rheumatoid Arthritis	Phase II	Isis
ISIS 104838 (P, T)*	TNF-alpha	Psoriasis	Phase II	Isis
OGX-011 (ISIS 112989) (P)*	Clusterin	Cancer—Solid Tumors	Phase I/II	Isis/OncoGenex
ISIS 113715 (P)*	PTP-1B	Diabetes	Phase I	Isis
ATL 1102 (ISIS 107248)*	VLA-4	Multiple Sclerosis,	Phase I	Antisense Therapeutics

		Inflammatory Diseases		Limited
ISIS 301012 (P)*	apoB-100	Cardiovascular	Phase I	Isis
LY2181308 (P) *	Survivin	Cancer	Preclinical	Lilly

(1) I = Intravitreal; P = Parenteral; T = Topical; O = Oral; E = Enema

(2) A compound in the preclinical phase of development is one in which we have initiated toxicology and pharmacokinetic studies in animals to support the filing with the FDA of an Investigational New Drug, or IND.

(3) Novartis Ophthalmics AG has the exclusive worldwide rights to distribute Vitravene.

* Drugs based on second-generation chemistry

The following section provides more detailed descriptions of our approved product and those products in clinical development and the disease indications they target. We also have a significant research program which we expect to yield additional development candidates in the future.

Cytomegalovirus, or CMV Retinitis

Individuals with suppressed immune systems, such as those with AIDS resulting from the HIV virus, are susceptible to opportunistic infections caused by CMV. Among patients with AIDS, CMV

retinitis is the primary cause of blindness. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet, cidofovir and fomivirsen.

Vitravene, or fomivirsen—In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Vitravene is an antisense compound that we discovered and developed. Novartis Ophthalmics AG, the eye health unit of life sciences leader, Novartis AG, and our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. Over the last several years, this has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis AG currently offers Vitravene on a limited basis in the U.S.

Cancer

We, together with our partners, are pursuing the development of antisense drugs for the treatment of a variety of cancers. In our clinical trials, we have observed evidence of activity of our drugs. In addition, patients tolerated our compounds well, with none of the serious side effects, such as bone marrow or immune system suppression, gastrointestinal distress or hair loss, associated with standard cancer chemotherapies.

Affinitak—Affinitak, which we licensed to Lilly in August 2001, is our antisense compound in Phase III clinical development for non-small cell lung cancer. Affinitak inhibits the production of one particular isotype, the alpha isotype, of protein kinase C, or PKC. PKC alpha is a member of a family of proteins that are associated with both normal and abnormal cell growth. PKC alpha has been shown to be involved in cancer cell growth and maintenance. In preclinical studies, we have been able to specifically inhibit the production of the PKC-alpha isotype without inhibiting the production of other isotypes, thus allowing the inhibition of an isotype believed to be involved in abnormal cell growth without more broadly affecting all the different PKC isotypes.

In 2003, we announced the results of our Phase III clinical trial of Affinitak in combination with traditional cancer chemotherapy drugs to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in a primary log-rank analysis of overall survival, the primary endpoint of the trial, of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone. Further, we performed additional analysis of the data using other standard statistical methods or tests. We observed that survival of the Affinitak treated patients was greater than that of the patients who received the chemotherapy alone. Another potentially important observation from the trial was that those patients who completed the prescribed course of therapy, six cycles, experienced a survival benefit compared to those patients who did not complete therapy. This result suggests that the duration of treatment with Affinitak may contribute to improved survival. Additionally, in those patients who completed the prescribed course of therapy, results favored the Affinitak group across multiple secondary endpoints, including time to disease progression, time to treatment failure and duration of remission.

The addition of Affinitak to carboplatin and paclitaxel was well tolerated. There were no increases in severe toxicities or toxicity related deaths in patients receiving Affinitak, compared to those receiving the chemotherapy alone. The most common side effects among patients in the study were fatigue and nausea. Patients in the study receiving Affinitak in combination with the chemotherapy had a higher rate of moderate thrombocytopenia, nausea and vomiting. Further, because clinicians administer Affinitak via continuous intravenous infusion, Affinitak treated patients had a higher incidence of catheter-related infections.

Lilly and we completed an analysis of the data from this trial and presented a summary of the findings at the 39th Annual Meeting of the American Society of Clinical Oncology in June 2003. In a

second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which most likely will occur in the second half of 2004.

OGX-011—OGX-011, also called ISIS 112989, is a second-generation antisense inhibitor of clusterin, which we are co-developing and commercializing with OncoGenex Technologies Inc., or OncoGenex, a Canadian oncology-focused research and development company. We have designed OGX-011 to inhibit the secretory protein clusterin, which acts as a cell-survival protein that is over-expressed in response to tumor killing strategies, like chemotherapy, hormone ablation and radiation therapy. Based on analysis of human tumor tissue, clusterin is over-expressed in several cancers, including prostate, breast, renal, bladder, non-small cell lung and ovarian. By inhibiting clusterin, clinicians intend to enhance the effects of drug therapies in the treatment of these cancers.

In preclinical animal studies, scientists from both OncoGenex and Isis, in collaboration with the Prostrate Center at Vancouver General Hospital, demonstrated OGX-011 improved the potency of traditional chemotherapies more than ten-fold in prostate cancer, without compromising safety. These studies also show that OGX-011, when combined with other cancer treatments in preclinical model systems, may significantly improve tumor reduction and delay disease progression in prostate, lung, bladder and renal cancer. These findings support the continued development of OGX-011 in combination with standard chemotherapy and other agents.

OncoGenex and we initiated a Phase I/II program of OGX-011 in patients with prostate cancer in December 2002. This Phase I trial is evaluating OGX-011 in combination with hormone ablation therapy prior to surgical removal of the prostate. In April 2003, Oncogenex and we initiated a second Phase I/II trial to evaluate OGX-011 in combination with TAXOTERE® in various solid tumors. We expect to report data from both clinical trials in the first half of 2004. OGX-011 is our first second-generation antisense anti-cancer drug in clinical trials.

LY2181308—We licensed our preclinical anti-cancer candidate, LY2181308, formerly ISIS 23722, to Lilly in 2002, as part of the expansion of our Lilly research collaboration into cancer. The compound targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin is one of the most abundantly expressed proteins in cancers. Our researchers and collaborators have shown that inhibiting expression of survivin by LY2181308 inhibits the growth of cancer cells. Since normal cells in the body do not express survivin, we expect that this drug will have fewer side effects than traditional chemotherapy.

In April 2003, we earned a $1.5 million milestone from Lilly in the development of LY2181308 as part of our research collaboration oncology expansion with them. LY2181308 is the first compound from this partnership that Lilly has selected for clinical development. We expect Lilly to initiate Phase I trials of LY2181308 during 2004.

ISIS 2503—Substantial evidence exists supporting a direct role for *ras* gene products in the development and maintenance of human cancer. *Ras* proteins are involved in passing information between cells. Ras, in both normal and mutated forms, is associated with abnormal cell growth and, as such, is associated with cancer. Cell culture and animal models have shown that ISIS 2503, a potent selective inhibitor of Harvey ras, or H ras, inhibits abnormal cell growth.

During 2002, we completed Phase I studies that demonstrated that ISIS 2503 was well tolerated and reported no serious side effects. We also observed evidence of activity. These results supported continued development of ISIS 2503 in Phase II trials for the treatment of pancreatic and breast cancer; however, during 2003 we decided to discontinue development of ISIS 2503 in order to focus our development resources on other drugs in our pipeline. We will continue to pursue partnership opportunities for ISIS 2503.

Inflammatory Diseases

Our research and development efforts in the therapeutic area of inflammatory diseases focus on identifying and developing antisense inhibitors to proteins such as intercellular adhesion molecule 1, or ICAM-1, another adhesion molecule called CD49d, which is a subunit of VLA-4, and tumor necrosis factor-alpha, or TNF-alpha. Researchers believe that these proteins are involved in inflammatory diseases.

Alicaforsen (ISIS 2302)—The most advanced compound in our cell adhesion program selectively inhibits ICAM-1 gene expression. ICAM-1 is a member of the adhesion molecule family. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, such as rheumatoid arthritis, asthma, psoriasis and inflammatory bowel diseases. Experts believe that ICAM-1 contributes to the pathology of these diseases and conditions. We are currently evaluating alicaforsen in two Phase III studies for the treatment of Crohn's disease. Additionally, we are conducting Phase II studies of alicaforsen enema formulation for the treatment of ulcerative colitis. According to the Crohn's and Colitis Foundation of America, up to one million people have inflammatory bowel disease, with occurrences evenly split between Crohn's disease and ulcerative colitis, or UC. According to the European Federation of Crohn's and UC Associations, inflammatory bowel disease affects a similar number of people in Europe.

- ***Crohn's disease***—Crohn's disease is a serious inflammatory disease that affects the entire digestive tract. A patient with Crohn's disease suffers chronic and often severe episodes of diarrhea, abdominal pain, rectal bleeding and fever. Two Phase III trials of alicaforsen in people with active Crohn's disease are in progress. One is enrolling patients in North America and the other in Europe, with a total of 300 patients in the two studies. These studies are evaluating the safety and efficacy of alicaforsen. We expect to report results of these trials in the second half of 2004.

  In October 2002, we reported results of an open-label Phase II clinical trial in patients with Crohn's disease showing that alicaforsen may produce clinical disease remissions. In late 1999, we completed a 300-patient pivotal trial of alicaforsen in Crohn's disease, which we initiated based on positive results from an earlier Phase II trial. The initial analysis of the data from the 300-patient trial did not show efficacy and the data did not support an NDA filing. However, further analysis of the data indicated that those patients who received higher exposure to alicaforsen were more likely to experience complete clinical remission of their disease, which was the primary endpoint of the pivotal trial. The current Phase III trials are in response to this additional analysis and patients are receiving higher doses of alicaforsen than previously studied in controlled trials.

- ***Ulcerative Colitis***—UC is an inflammatory disease of the colon, a part of the large intestine. Inflammation and ulceration of the innermost lining of the colon characterize UC. Symptoms typically include diarrhea, rectal bleeding and abdominal pain. UC differs from Crohn's disease, as it affects only the colon.

  In October 2001, we reported that data from a Phase II clinical trial demonstrated that alicaforsen improved symptoms of patients with UC. Patients receiving an enema formulation of alicaforsen experienced a dose-dependent reduction in disease activity index score, or DAI, and clinical activity index score, or CAI. Further, many of these patients did not require additional medical and surgical intervention during the six month study period. The DAI and CAI measure the signs and symptoms that patients with ulcerative colitis typically experience. Clinical investigators observed no serious side effects in patients in this Phase II trial. Based on these favorable results, in November 2002 we launched a multi-center Phase II trial in the U.S. We designed this 170-patient U.S. study to compare the safety and efficacy of an enema formulation of alicaforsen to mesalamine enema, a widely used medication for ulcerative colitis. We expect

to complete enrollment in this trial in early 2004. In April 2003, we initiated a randomized, double-masked, placebo-controlled Phase II trial in 100 patients in the U.S. and Europe. The primary endpoint was to study improvement in the Disease Activity Index (DAI) upon completion of the six-week dosing period. We plan to report data from both the 170-patient and 100-patient clinical trials in the second half of 2004.

- ***Pouchitis***—Pouchitis is an inflammation of the ileo-anal pouch and is a common complication in ulcerative colitis patients requiring surgical removal of the diseased colon. Pouchitis is a disorder without satisfactory medical therapy. Symptoms include an increased number of stools, rectal bleeding, abdominal cramping and fever. Pouchitis affects a relatively small number of individuals who have inflammatory bowel disease. We conducted a Phase II trial of an enema formulation of alicaforsen for the treatment of patients with pouchitis. We designed the 12-patient trial to evaluate the safety and efficacy of alicaforsen in patients with pouchitis. In May 2003, we reported that interim data from the first eight patients in this trial demonstrated an improvement in clinical disease symptoms after receiving treatment of an enema formulation of alicaforsen, and that clinical investigators observed no significant adverse events. In October 2003, we reported additional data from this clinical trial that demonstrated sustained improvement of up to nine months, based on endoscopic scores that measured the physical signs of inflammation in the lower bowel, and that alicaforsen was well-tolerated.

ISIS 104838—ISIS 104838 is a second-generation antisense inhibitor of TNF-alpha and the first product from our proprietary second-generation chemistry to enter the clinic. TNF-alpha, or tumor necrosis factor alpha, is a naturally occurring cytokine that is implicated in the development and progression of many inflammatory, infectious and autoimmune diseases, including rheumatoid arthritis and psoriasis. TNF-alpha is involved in bone and cartilage absorption, facilitates inflammation and inhibits bone formation. Most patients with rheumatoid arthritis have high levels of TNF-alpha.

- ***Rheumatoid Arthritis***—According to the Arthritis Foundation, rheumatoid arthritis affects 2.1 million Americans, mostly women. Rheumatoid arthritis is a systemic disease that affects the entire body and is one of the most common forms of arthritis. Inflammation of the membrane lining in the joint, or synovium, which causes pain, stiffness, warmth, redness and swelling, is a characteristic symptom of rheumatoid arthritis. The inflamed synovium can invade locally causing damage to bone and cartilage. Inflamed cells release enzymes that may digest bone and cartilage. The involved joint can lose its shape and alignment, resulting in pain and loss of movement.

  We recently reported data from a Phase II clinical trial which demonstrate that ISIS 104838 produced disease response in patients with rheumatoid arthritis. In the randomized, placebo-controlled trial, 157 evaluable patients received subcutaneous injections of either placebo or one of the three dose regimens of 200mg of ISIS 104838. Patients receiving once- and twice-weekly treatments experienced similar responses, with 41% of evaluable patients achieving a 20% decrease in disease activity, or ACR 20, as compared to 23% of placebo-treated patients achieving ACR 20. No drug-related serious adverse events were reported from this trial. The most frequent adverse event was injection site reaction. The reactions were generally considered mild in nature and occurred principally in the first month of treatment and with similar frequency as reported for protein therapeutics.

  In October 2003, we reported the final results of our first Phase II clinical trial of ISIS 104838 in 20 patients with rheumatoid arthritis. The results demonstrated that 104838 reduced TNF-alpha mRNA levels in synovial tissue and stabilized levels of TNF-alpha in blood, and that ISIS 104838 was well tolerated. We designed this clinical trial to study the ability of different concentrations of ISIS 104838 to reduce TNF-alpha levels in blood and synovial tissue. We plan

to initiate an additional Phase II clinical trial during 2004 to further explore dose, schedule and treatment duration of ISIS 104838 in patients with rheumatoid arthritis.

As we reported in 2001, Phase I trials of intravenous infusion and subcutaneous injection of ISIS 104838 demonstrated the potential for a more convenient dosing schedule of once every two to four weeks as well as safety advantages over first-generation antisense drugs. The subcutaneous study demonstrated substantial improvement in local tolerability over first-generation antisense drugs.

We believe that the positive results from the clinical data on ISIS 104838 helps to validate the potential of second-generation antisense drugs overall, and that these results will be useful to advance the development of all our second-generation drugs, since all antisense drugs of a chemical class behave similarly.

The development of an oral formulation of ISIS 104838 had been the focus of our Orasense joint venture with Elan. At the end of 2002, Elan concluded its participation in the Orasense collaboration, in conjunction with its restructuring efforts. As a result, we regained all rights to ISIS 104838, with a potential nominal royalty due to Orasense. We are continuing to advance the development of oral formulation platform technology.

- ***Psoriasis***—According to the National Psoriasis Foundation, more than 7 million people in the United States have psoriasis, which is a non-contagious disorder of the skin. Abnormal growth or overproduction of skin cells characterizes psoriasis. The most common type is plaque psoriasis, which accounts for 80% of psoriasis diagnosis. We have completed a Phase II clinical trial of a topical formulation of ISIS 104838 in patients with psoriasis and have concluded that the data are not sufficient to support continued development of the current topical formulation. We are planning a Phase II trial of systemically delivered ISIS 104838 for the treatment of psoriasis.

ISIS 107248—ISIS 107248, or ATL 1102, is a second-generation antisense inhibitor of CD49d, which is a subunit of VLA-4. Studies in animal models have demonstrated that inhibition of VLA-4 has a positive effect on a number of inflammatory diseases like multiple sclerosis. In December 2001, we licensed ISIS 107248 to Antisense Therapeutics Limited, or ATL. Under our agreement with ATL, we completed the required preclinical studies for ISIS 107248 and manufactured the bulk drug for human clinical trials at ATL's expense. ATL is responsible for the future clinical development and the commercialization of the drug. In August 2003, ATL initiated a Phase I clinical trial of ISIS 107248 for the treatment of multiple sclerosis. We expect that ATL will report final data from this trial mid-year 2004, and plan to initiate a Phase II trial in patients with multiple sclerosis by the end of 2004.

Hepatitis C, or HCV

HCV represents a major public health challenge. This potentially deadly disease affects the liver and can eventually cause liver cirrhosis and death. HCV affects an estimated four million people in the United States, and will kill 10,000 to 12,000 people in the United States each year. Physicians attempt to eradicate this virus from chronically infected individuals by using Interferon-alpha therapy, either alone or in combination with the drug ribavirin. According to data from

the National Institute of Health, patients with genotypes 2 and 3 are two to three times more likely to respond to interferon based therapy than patients with genotype 1. Genotype 1 is the most common genotype in the United States. Better, safer and more effective treatments for HCV are urgently needed, as current therapies have limited efficacy and potentially serious side effects.

ISIS 14803—Our antisense inhibitor of HCV, ISIS 14803, may represent a significant therapeutic advance in treating this serious viral epidemic. We designed ISIS 14803 to inhibit the replication of HCV.

Two clinical trials of ISIS 14803 have demonstrated activity in patients with HCV, and a third clinical trial is in process. Isis presented data from two single agent studies that showed ISIS 14803 is active in drug resistant, genotype 1 HCV patients, the most difficult-to-treat segment of the HCV patient population. In a four-week Phase I/II clinical trial initiated in August 2003, which we designed to evaluate both the safety and efficacy of ISIS 14803 in patients with HCV, ISIS 14803 demonstrated dose-dependent antiviral activity, decreasing the level of virus in the blood in patients with drug resistant chronic HCV. All patients in the clinical study had the most common and drug resistant form of HCV, genotype 1, and all but one patient had failed previous interferon-based therapy. Flu-like symptoms, headache and fatigue were the most common side effects observed in the trials. In October 2003, we reported the final results of a 43-patient single agent Phase II clinical trial that demonstrated promising antiviral activity by producing up to 3.8 log dose-dependent reductions in plasma virus levels in five of 17 patients with HCV.

In May 2003, we initiated a 30-patient Phase II clinical trial to assess the benefits of adding ISIS 14803 to standard treatments for HCV. We designed the trial to explore the activity of ISIS 14803 in combination with standard HCV treatments based on cumulative experience with the drug as a single agent. We plan to announce initial results from this study in the second half of 2004.

Metabolic Diseases

We are pursuing the discovery and development of antisense drugs for metabolic diseases such as diabetes and obesity. These chronic diseases affect millions of people and represent significant areas of unmet medical need. We believe that our second-generation antisense drugs will have properties that will make them attractive therapies.

ISIS 113715—ISIS 113715 is our second-generation antisense inhibitor of the PTP-1B gene for type 2 diabetes. According to the American Diabetes Association, diabetes affects more than 18 million people and type 2 diabetes constitutes 90 percent of those cases. An antisense inhibitor of PTP-1B represents a new approach to the treatment of diabetes. For years, pharmaceutical companies interested in diabetes research have actively pursued phosphatases, such as PTP-1B, as part of traditional small molecule drug discovery efforts. However, due to structural similarities among closely related enzymes, it is often difficult to identify small molecule drugs with the degree of specificity that the antisense approach can obtain.

The preclinical studies of ISIS 113715 demonstrated compelling activity in multiple diabetic animal models and suggested activity as an insulin sensitizer without causing hypoglycemia and while reducing cholesterol and weight gain.

In May 2003, we initiated a Phase I clinical trial to assess the safety and pharmacokinetic profile of several doses of ISIS 113715 by parenteral administration in 20 healthy volunteers. In September 2003, we reported the results from this Phase I study, which demonstrated improved glucose tolerance and increased insulin sensitivity in all patients who received ISIS 113715, and that ISIS 113715 was well tolerated.

Based on the results of the Phase I study, we are initiating a Phase II clinical trial to further evaluate the drug's ability to regulate blood sugar levels in patients with type 2 diabetes. We plan to initiate enrollment by mid-2004 and report data from this clinical trial in late 2004 or early 2005.

ISIS 13650—ISIS 13650 is an inhibitor of c-*raf* kinase for the treatment of diabetic retinopathy and age-related macular degeneration. Diabetic retinopathy is an ocular complication of diabetes. The incidence of these conditions continues to grow with the advancing age of the U.S. population. In preclinical studies, antisense inhibition of c-raf kinase is associated with a reduction of neovascularization, or growth of blood vessels, which can obstruct vision. During 2002, ISIS 13650, a second-generation antisense product, was in preclinical development. During 2003, we decided not to

invest any further in the development of ISIS 13650. This action is part of our broader decision to pursue ophthalmic research through partnerships rather than using our own resources.

Cardiovascular Diseases

Cardiovascular disease is the leading cause of death in the United States, according to the National Institutes of Health. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Statistics from the American Heart Association show more than 100 million American adults have high cholesterol levels.

ISIS 301012—ISIS 301012 is the newest compound that we have added to our pipeline. It targets apoB-100, a molecule that has been of great interest to the industry, yet has long been considered "undruggable" by traditional small molecule approaches. ApoB-100 is a protein that plays a pivotal role in the production of low-density lipoprotein (LDL), the "bad" cholesterol. In preclinical studies, ISIS 301012 reduced total cholesterol, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and triglyceride levels, all of which are keys to managing heart disease. We initiated a double-blind, placebo-controlled, dose escalation Phase I study in late 2003. The goal of this trial is to assess the safety, tolerability and pharmacokinetic profile of ISIS 301012, and its ability to reduce several components of cholesterol that are important in the management and prevention of cardiovascular disease. We plan to report data from this study in the second half of 2004.

Research Programs

We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drug candidates. The goal of our target-based research programs is to identify antisense and small molecule drug candidates to treat diseases for which there are substantial markets and for which there is a need for better drugs. In addition, our research programs focus on identifying next-generation compounds to serve as backup compounds to our current products in development and to our development candidates. Our Ibis program focuses on developing mass spectrometry-based technology for identifying and treating infectious diseases.

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. Through these programs, we can efficiently explore numerous disease targets and identify lead compounds to advance into preclinical development. We are currently pursuing antisense and small molecule drug discovery programs focused on various anti-viral and anti-bacterial targets, inflammatory disease targets, cardiovascular disease targets and other key molecular targets that might play critical roles in cancer and metabolic diseases like diabetes and obesity.

We are pursuing three early-stage antisense mechanisms, including RNA interference, or RNAi, micro-RNA, and alternative splicing, through research collaborations and partnerships like those we have with Ercole Biotech, Inc., or Ercole, and Alnylam Pharmaceuticals, Inc., or Alnylam.

RNAi is an antisense mechanism that involves using a small interfering RNA, or siRNA, an antisense inhibitor, as a method to target an mRNA sequence. With siRNA, the cell recruits a protein group called RISC to prevent the production of a disease-causing protein. We have a strong intellectual property position in RNAi methodology and are pursuing opportunities to license these patents to companies specializing in RNA interference as a therapeutic method.

Micro-RNAs are an emerging class of drug targets and a new area for drug discovery. Micro-RNAs are small RNA molecules that appear to have critical functions in controlling the process of gene expression. Micro-RNAs can serve as drug targets or as drugs themselves. Researchers estimate that there are approximately 250-300 known micro-RNA molecules in humans.

Modulation of alternative splicing seeks to control the process by which a single gene can lead to several proteins. To be converted into proteins, genes must be initially copied into a pre-mRNA. This pre-mRNA then undergoes splicing, a process where stretches of RNA are deleted and the remaining RNA strand is then linked back together. Splicing is necessary for a messenger RNA, or mRNA, to be read by the cell to produce a particular protein.

Collaborative Arrangements and Licensing Agreements

Our strategy is to use alliances with other companies and equity-based financing to increase our financial resources, reduce risk, and retain an appropriate level of ownership of products currently in development. Through alliances with major pharmaceutical companies and biotechnology companies, we can obtain funding, expand existing programs, learn of new technologies, and gain additional expertise in developing and marketing products.

2003 and Recent Business Development Highlights

We are focused on establishing new partnerships and on advancing and building upon existing relationships. We currently have agreements with more than a dozen partners. These span all four areas of our business: antisense drug discovery and development, GeneTrove, Ibis and our intellectual property estate. The following is a list of our business development highlights for 2003 and early 2004.

- We received a grant and subsequently achieved two milestones in our antisense drug discovery partnership with the Industrial Technology Research Institute, or ITRI, of Taiwan, focused on the coronavirus associated with Severe Acute Respiratory Syndrome, or SARS.
- We received a grant from the Singapore Economic Development Board, or Singapore EDB, to support the broadening of two of our RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS.
- We received a grant from the CDC to develop and apply Ibis' TIGER technology to the surveillance of infectious diseases in the U.S.
- We expanded our drug discovery partnership with OncoGenex to include the development of OGX-225, a second-generation antisense anti-cancer drug that we are developing to inhibit the production of two related proteins simultaneously.
- We initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing with Ercole Biotech, Inc., or Ercole. Ercole licensed Isis' Bcl-x preclinical antisense drug as its lead development compound.
- We achieved a $1.5 million milestone from Lilly for the selection of LY2181308, an inhibitor of survivin, for clinical development.
- We achieved a second milestone in our antisense drug discovery collaboration with Amgen.
- We entered into a target validation agreement with Pfizer, Inc., in which Pfizer obtained access to our antisense inhibitors and acquired a license to specific patents within our intellectual property estate for use in its internal antisense-based functional genomics program.
- We received a two-year contract from DARPA providing up to $19.5 million to further development of our TIGER biosensor under our collaboration with SAIC.
- We entered into a strategic alliance with Alnylam to develop and commercialize RNA; therapeutics, and made an equity investment in Alnylam.

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 Affinitak, our antisense drug which Lilly is testing in a Phase III trial 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. In 2002, Lilly and we expanded this collaboration to include oncology and the license of LY2181308, formerly ISIS 23722, our antisense inhibitor of survivin.
- Lilly committed to lend us, interest-free, up to $100.0 million over a four-year period to fund our obligations under the research collaboration. We can repay this loan at our option in either cash or our common stock, at a fixed conversion price of $40 per share.

To date, Lilly has paid or committed to pay us more than $200.0 million in funding through 2005, including the $100.0 million loan, the $75.0 million equity investment, the $25.0 million in Affinitak up-front license fees, and amounts for the remaining Affinitak development costs. Assuming the success of multiple products from our collaboration with Lilly, we have the opportunity to earn additional future milestones and royalties from Lilly that could be substantial to us.

In September 2002, we further expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we upgraded and expanded our manufacturing facility, including the addition of a new state-of-the-art manufacturing suite. Lilly provided us with funding in the form of a $21.2 million loan to build the new suite. In June 2003, we reached a mutually beneficial renegotiation of our manufacturing relationship with Lilly. Lilly waived repayment of the $21.2 million manufacturing loan it provided us to build the new manufacturing facility. Lilly also agreed to allow us to use the facility to manufacture other drugs. In exchange, we released Lilly from its obligations to purchase additional product from us and its obligation to pay for the costs of maintaining an idle manufacturing suite.

In April 2003, we earned a $1.5 million milestone from Lilly in the development of LY2181308, the antisense inhibitor of survivin, as part of the research collaboration oncology expansion. LY2181308 is the first compound from the partnership to be selected for clinical development by Lilly. We expect Lilly to initiate Phase I trials of LY218308 during 2004.

In July 2003, we expanded the cancer research component of our antisense drug discovery collaboration with Lilly to include multiple antisense mechanisms, such as RNAi and alternative splicing, as well as alternative chemistries, such as Peptide Nucleic Acid, or PNA. We are currently jointly developing antisense drugs with Lilly that work through an RNAi mechanism or use our PNA chemistry as potential follow-on drugs to LY2181303.

Our relationship with Lilly has historically provided several revenue sources, including research funding related to their $100.0 million research loan to us, development milestones, and revenue related to Affinitak. During 2003, 2002 and 2001, we generated revenue from our relationship with Lilly totaling $30.9 million, $45.4 million and $14.5 million, respectively, which comprised 62%, 57%, and 27%, respectively, of our total revenue during those same periods.

Antisense Drug Discovery Collaborations

Amgen

In December 2001, we entered into a three-year collaboration with Amgen to discover new antisense drugs. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration. If drugs from the collaboration are successful, we will receive milestone payments upon key clinical and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. In August 2002 and February 2003, we earned progress-related research milestones under this drug discovery collaboration.

Ercole Biotech, Inc.

In May 2003, we and Ercole Biotech, Inc. initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, we cross-licensed our respective splicing-related intellectual property. We are combining our alternative splicing expertise with Ercole to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, we granted Ercole a license to our Bcl-x molecule and certain of our chemistry patents. In addition, we took an equity ownership position in Ercole, with the initial funding in the form of convertible debt, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. We also have the option to make an additional equity investment in Ercole.

Industrial and Technology Research Institutes of Taiwan

In June 2003, we initiated a collaboration with ITRI to identify antisense candidates targeting the coronavirus associated with SARS. We conducted the research in exchange for an upfront payment of $1.0 million, milestone payments, and the potential for future funding. In December 2003, we achieved two milestones in our antisense drug discovery partnership with ITRI, for which we received a total of $1.0 million. The milestones related to the identification of second-generation antisense drugs that inhibit SARS virus replication and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs as specified under the agreement.

Singapore Economic Development Board

In November 2003, we received a grant of up to $8.0 million over three years from the Singapore Economic Development Board which will fund, in part, the broadening of two of our RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS. In connection with this grant, we established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary of Isis Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. We will retain rights to a limited number of RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. In addition, Alnylam and we will share the proceeds of any licenses Alnylam grants under its previously announced Interfe*Rx*™ program that include sublicenses to our patents. We also made a $10 million equity investment in Alnylam and have agreed to provide Alnylam with access to our resources for development and commercialization of RNAi therapeutics, including process development, bioanalytic methods, quality control, and manufacturing.

In turn, Alnylam nonexclusively licensed us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

We are focused primarily on discovering and commercializing single-stranded antisense drugs that work through a variety of mechanisms, including RNAi and RNase H. This alliance strengthens Alnylam's position in double-stranded RNAi and gives Isis the ability to share in Alnylam's success in this area.

Antisense Drug Development Collaborations

An important aspect of our business model is to selectively extend our expertise and intellectual property position in antisense technology to industry partners that are interested in developing antisense therapeutics. In return for providing companies with access to our technology, we receive an ownership interest in the resulting products and/or in the companies. This provides us with the opportunity to create a much broader antisense pipeline than we could afford to develop on our own while minimizing our financial obligations. We have implemented this integral component of our strategy through our partnerships with major pharmaceutical companies and with ATL, OncoGenex and Santaris Pharma A/S, or Santaris, formerly Pantheco A/S, or Pantheco. Our partnerships with OncoGenex, ATL and Santaris represent our ability to broaden the reach of antisense technology in emerging companies globally. We believe we will have more of these opportunities that, when combined with our own antisense drug pipeline, will allow us to participate in the establishment of a new sector of the pharmaceutical industry based on antisense technology.

Antisense Therapeutics Limited

ATL 1102, or ISIS 107248, has been demonstrated to have positive effects in animal models for the treatment of certain inflammatory diseases such as multiple sclerosis. In December 2001, we licensed ISIS 107248 to ATL, an Australian company publicly traded on the Australian Stock Exchange. We were responsible for completing the required preclinical studies for ISIS 107248 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug. In August 2003, ATL initiated a Phase I clinical trial of ISIS 107248 for the treatment of multiple sclerosis, and will report final results in mid-2004. ATL plans to initiate a Phase II study in the second half of 2004. In addition, we are participating with ATL in a five-year antisense drug discovery and development collaboration. ATL will pay us for access to our antisense expertise and for research and manufacturing services we provide them during the collaboration. Additionally, ATL is obligated to pay us royalties on any antisense drugs discovered and developed within the partnership. We currently own approximately 11% of ATL's equity and hold options for additional shares. If all of ATL's outstanding options, including ours, were exercised, our ownership in ATL would be approximately 14%.

OncoGenex Technologies Inc.

In November 2001, we established a drug development collaboration with OncoGenex Technologies Inc., a Canadian oncology-focused research and development company, to co-develop and commercialize OGX-011, or ISIS 112989, an anti-cancer antisense drug candidate. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target clusterin, with our proprietary

second-generation antisense chemistry. We conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. We also manufactured OGX-011 for preclinical and Phase I/II studies. OncoGenex has responsibility to perform Phase I clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and to perform Phase I/II clinical trials in combination with standard chemotherapy in patients with solid tumors known to express clusterin, including non-small cell lung, prostate, breast, renal, and ovarian cancers. In December 2002, OncoGenex and we announced the initiation of a Phase I clinical trial of OGX-011 in patients with prostate cancer. In April 2003, OncoGenex and we initiated a second phase I clinical study of OGX-011 in combination with TAXOTERE® in patients with solid tumors. We expect to report data from both clinical trials in the first half of 2004. OGX-011 is our first second-generation antisense anti-cancer drug in human clinical trials.

In September 2003, OncoGenex and we expanded our antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug candidate, OGX-225. OncoGenex has responsibility for the preclinical and clinical development of the drug. OncoGenex issued us OncoGenex securities as payment for an upfront fee. In addition, OncoGenex agreed to provide to us milestone payments for key clinical and regulatory achievements and royalties on product sales. As of December 31, 2003, our ownership interest in OncoGenex was less than 10%.

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1998 and September 2000, we entered into license agreements with Santaris, formerly Pantheco. We amended the agreements in May 2003. Under the terms of the amended and restated license agreement, we licensed our novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to our approval. Santaris has agreed to pay us royalties on any products developed under the license.

As part of our original license agreements with Pantheco, we received shares of Pantheco common stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, we purchased additional shares of Pantheco for $55,000 as a result of antidilution provisions related to Pantheco's stock. After the merger and as of December 31, 2003, our ownership interest in Santaris was less than 10%.

Antisense Commercialization

Novartis Ophthalmics AG

In 1997, we entered into an agreement with Novartis Ophthalmics AG, formerly CIBA Vision Corporation, granting them exclusive worldwide distribution rights for Vitravene, an antisense compound that we discovered and developed. The terms of the agreement provided for us to receive $20.0 million in pre-commercial fees and milestones. As of December 31, 2001, we had received the full $20.0 million of these pre-commercial fees and milestones. In August 1998, the FDA approved Vitravene to treat CMV retinitis in AIDS patients. Novartis Opthalmics AG launched Vitravene in November 1998. Due to the low incidence of CMV retinitis among patients with AIDS, Novartis AG currently offers Vitravene on a limited basis in the U.S.

GeneTrove Collaborations

Our GeneTrove program uses our antisense technology as a tool to provide important information about the function of genes and has automated the initial steps in our antisense drug discovery process. Our current focus is to use GeneTrove information to direct our own drug discovery research and that of our antisense drug discovery partners, like Lilly and Amgen. We also offer antisense-based gene function information and license our antisense based functional genomics patents to pharmaceutical

company partners that are evaluating the genes as targets for their own drug discovery programs. During 2003, we entered into a target validation agreement with Pfizer, Inc., in which Pfizer obtained access to our antisense inhibitors and acquired a license to specific patents within our intellectual property estate for use in its internal antisense-based functional genomics program.

Ibis Collaborations

We have entered into numerous contracts and grants with various government agencies to complete research and development work for defense against biological warfare attacks and threat scenarios. To date, our Ibis program has been awarded government contracts and grants representing potential funding of up to $55.0 million. The contracts and grants include a multi-year contract with DARPA, a three-year contract with USAMRIID, a three-year grant from the CDC and a one-year grant from the FBI.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Integrated DNA Technologies, Inc.

In March 1999, we established a long-term research-scale antisense inhibitor supply agreement with Integrated DNA Technologies, Inc., or IDT. IDT is a leading supplier of antisense inhibitors used in research. Additionally, we further solidified our intellectual property leadership position in antisense technology by broadening our license to certain antisense patents from IDT. In this long-term supply agreement, IDT agreed to manufacture research-scale antisense inhibitors and research reagents to our specifications. We paid IDT $5.0 million toward our future purchase of antisense inhibitors. As of December 31, 2003, the balance of our prepayment was approximately $4.3 million. In December 2001, we expanded our existing licensing agreement with IDT on certain patents that are useful in functional genomics and in making certain antisense drugs. The expanded license allows us to exclusively sublicense this intellectual property for functional genomics purposes. We have paid IDT $4.2 million through December 31, 2003 and expect to pay IDT an aggregate of $700,000 over the next two years for the license.

Hybridon, Inc.

In May 2001, we entered into an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to our suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, we paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in our common stock before May 2003. In return for access to our patents, Hybridon agreed to pay us $6.0 million in Hybridon common stock before May 2004. In September 2001 and October 2001, we issued to Hybridon 357,143 shares of our common stock valued at $5.0 million and 500,000 shares of our common stock valued at $10.0 million, respectively. In May 2002, Hybridon issued to us 1,005,499 shares of its common stock valued at $1.3 million and paid us $700,000 in cash. In August 2002, Hybridon and we cancelled the remaining reciprocal financial obligations related to this agreement. The cancellation of the obligations resulted in a decrease to our carrying value for the license in the amount of $500,000.

Molecular Biosystems, Inc.

In March 2001, we amended a non-exclusive Patent License Agreement, which we entered into with Molecular Biosystems, Inc. in September 1992. The amendment provided us with a fully paid-up

license to certain patents and patent applications in exchange for a one-time payment to Molecular Biosystems of $1.0 million.

Out-Licensing Arrangements

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech Pharmaceuticals, Inc., a publicly-held company, certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense compound intended for use in the treatment of ophthalmic diseases. Eyetech paid us a $2.0 million upfront fee and

agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us. In December 2002, Eyetech entered into an agreement with Pfizer to develop and commercialize Macugen. In 2003, Pfizer and Eyetech reported encouraging Phase III data for Macugen that Eyetech says will serve as the basis for an NDA, with commercialization of the drug expected in 2005. Assuming successful commercialization of Macugen, we have the opportunity to earn future milestone payments and royalties that could be substantial to us.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche, a business unit of Roche Diagnostics, for use in the production of Roche's diagnostic products. The royalty-bearing license grants Roche non-exclusive worldwide access to some of our proprietary chemistries, in exchange for initial and ongoing payments from Roche to us.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides, like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide compounds, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide compounds. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the compounds. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

In September 2002, we expanded our relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. Through this agreement we upgraded and expanded our manufacturing facility, including the addition of a new state-of-the-art manufacturing suite. Lilly provided us with funding in the form of a $21.2 million loan to build the new suite. In June 2003, we reached a mutually beneficial renegotiation of our manufacturing relationship with Lilly. Lilly waived repayment of the $21.2 million manufacturing loan it provided us to build the new manufacturing facility. Lilly also agreed to allow us to use the facility to manufacture other drugs. In exchange, we released Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from us and the obligation to pay for the costs of maintaining an idle manufacturing suite.

In addition, we have contractual obligations to manufacture clinical trial materials and/or commercial supply for Amgen, ATL, Lilly, Novartis and OncoGenex. We believe we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our

partners for commercial, research and clinical needs as well as meet our current internal research and clinical needs. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we will be able to manufacture antisense compounds at commercially competitive prices.

Patents and Proprietary Rights

Our success will depend, in part, on our ability to obtain patent protection for our products in the United States and other countries. We file applications, as appropriate, for patents covering our products and processes. As of March 3, 2004, we owned or had exclusively licensed more than 1,300 issued patents worldwide. Patents issued to us, applied for by us or exclusively licensed by us cover the following types of inventions, processes and products:

- Method claims for the use of RNA/DNA oligonucleotides and other antisense inhibitors, in gene functionalization and target validation, including chemistries, antisense inhibitor designs called "motifs", methods of use of antisense inhibitors and mechanisms of action by which antisense inhibitors inactivate an RNA target;
- Composition of matter claims to core chemistries for chemically modifying oligonucleotides, which cover our rights to the building blocks of our compounds;
- Composition of matter claims to antisense compounds targeted to particular RNA target sequences, which cover our drugs;
- Use claims for using oligonucleotides targeted to particular disease targets, which cover our right to use oligonucleotide-based drugs to treat specific diseases or modulate expression of the target gene;
- Method and composition of matter claims for the formulation and delivery of therapeutic oligonucleotides, which cover our pharmaceutical formulations of our drugs;
- Method claims for the manufacture of oligonucleotides, which cover our new, improved and/or more cost effective ways to manufacture oligonucleotides;
- Composition of matter claims to RNA structural elements, which cover our rights for discovery of small molecules that bind to these RNA structural elements;
- Method claims for analyzing the interaction of small molecules with RNA, which cover our novel discovery methods using mass spectrometry to analyze the interaction of small molecules with RNA;
- Method claims for optimizing the interaction of drug substances with their target molecules, which cover our mass spectrometry-based structural activity relationship discovery methods, by mass spectrometer;
- Method claims for identifying unknown bioagents utilizing mass-spectrometry-based analyses; and

- Method claims for rapidly discovering antisense oligomeric compounds, which cover our rapid throughput method of discovering antisense oligonucleotides.

Government Regulation

Extensive regulation by United States and foreign governmental authorities governs our manufacture and potential sale of therapeutics. In particular, pharmaceutical products are subject to rigorous preclinical and clinical testing and other approval requirements by the FDA in the United

States under the Federal Food, Drug and Cosmetic Act and by comparable agencies in most foreign countries. Various federal, state and foreign statutes also govern or influence the manufacture, safety, labeling, storage, record keeping and marketing of such products. State, local, and other authorities also regulate pharmaceutical manufacturing facilities.

In conjunction with obtaining approval of Vitravene, we successfully passed the manufacturing pre-approval inspection by the FDA and European regulatory authorities. Approval of each new drug will require a rigorous manufacturing pre-approval inspection by regulatory authorities.

In addition to regulations enforced by the FDA, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

We fund our Ibis program primarily through contracts or subcontracts with agencies of the U.S. Government. As a result, we must comply with various government regulations, including the Federal Acquisition Regulations, or FARs, and agency regulations supplemental to the FARs; the Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with certain contract negotiations; and laws, regulations and executive orders restricting the use and dissemination of information classified for national security purposes and the export of certain products and technical data.

Competition

For many of their applications, antisense-based drugs, as well as Ibis small molecules, will compete with existing therapies for market share. In addition, a number of companies are pursuing the development of oligonucleotide-based technology and the development of pharmaceuticals utilizing this technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies.

Vitravene and our other products under development address numerous markets. The diseases targeted by our drugs for which we may receive regulatory approval will determine our competition. For certain of our products, an important factor in competition may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market is an important competitive factor. We expect to compete among products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, reliability, availability, price and patent position.

A number of factors have affected the market for Vitravene, our antisense drug for CMV retinitis. Anti-HIV drugs that were introduced prior to Vitravene's approval, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis.

We currently have two drugs in Phase III trials. We licensed Affinitak, our antisense drug for non-small cell lung cancer, to Lilly in August 2001. Under our agreement with Lilly, Lilly is responsible for the commercialization of Affinitak. If future studies support commercialization, we expect that physicians would use Affinitak in combination with current standard chemotherapy regimens for non-small cell lung cancer. As such, we expect that it will be complementary to existing drugs for the treatment of non-small cell lung cancer rather than directly competitive. Our second drug in Phase III trials is alicaforsen, which we are studying in patients with Crohn's disease. Alicaforsen will likely compete with Johnson & Johnson's drug, Remicade, which is approved for the treatment of Crohn's disease and rheumatoid arthritis.

Employees

As of March 3, 2004 we employed 457 individuals, of whom 174 held advanced degrees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with its employees to be good.

Executive Officers

The following set forth certain information regarding our executive officers as of March 3, 2004:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	58	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, J.D.	48	Director, Executive Vice President, Chief Financial Officer and Secretary
C. Frank Bennett, Ph.D.	47	Vice President, Antisense Research
Richard K. Brown, Ph.D.	51	Vice President, Business Development
David J. Ecker, Ph.D.	49	Isis Vice President and President, Ibis Therapeutics
Arthur A. Levin, Ph.D.	50	Vice President, Development

Patricia Lowenstam	57	Vice President, Human Resources and Operations
Karen Lundstedt	39	Vice President, Investor Relations and Corporate Communications
John McNeil	39	Vice President, Informatics
Aron F. Stein, Ph.D.	45	Vice President, Regulatory Affairs and Quality Assurance

STANLEY T. CROOKE, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer

Dr. Crooke was a founder of Isis and has been its Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. He serves as a director of Antisense Therapeutics Ltd., a biopharmaceutical company, Axon Instruments, Inc., a developer and manufacturer of novel high-technology devices and software for drug discovery, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. Dr. Crooke is also an adjunct professor of pharmacology at the University of California, San Diego, and San Diego State University.

B. LYNNE PARSHALL, J.D.
Director, Executive Vice President, Chief Financial Officer, and Secretary

Ms. Parshall has served as a director of Isis since September 2000. She has served as our Executive Vice President since December 1995, our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP, counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is also a member of the Licensing Executives Society and a member of the American, California and San Diego bar associations.

C. FRANK BENNETT, Ph.D.
Vice President, Antisense Research

Dr. Bennett has served as our Vice President, Antisense Research since June 1995. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to

joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions.

RICHARD K. BROWN, Ph.D.
Vice President, Business Development

Dr. Brown joined Isis in June 2001 as President of the GeneTrove program and has been our Vice President, Business Development since January 2003. Prior to joining Isis, Dr. Brown was President of Irori, a company that develops, manufactures and markets combinatorial chemistry and medicinal chemistry products to the pharmaceutical industry. He joined Irori in 1996 and served as President from 1998 to June 2001.

DAVID J. ECKER, Ph.D.
Isis Vice President and President, Ibis Therapeutics

Dr. Ecker was a founder of Isis and has served as our Vice President & Managing Director of Ibis Therapeutics, a program of Isis Pharmaceuticals, since June 1995. In 2001 he assumed the role of President of the program. He served as our Vice President, Biology from July 1993 to June 1995, as our Executive Director, Molecular and Cellular Biology from February 1993 to July 1993, and as our Director, Molecular and Cellular Biology from February 1989 to February 1993. From 1984 until February 1989, he was employed by SmithKline and French Laboratories in a variety of research positions.

ARTHUR A. LEVIN, Ph.D.
Vice President, Development

Dr. Levin has served as our Vice President, Development since 1995. Prior to joining Isis, Dr. Levin worked at Hoffmann-La Roche Inc. where he was Research Leader in their Investigative Toxicology Department managing the Nuclear Receptor Research Group. During his tenure at Hoffman-LaRoche, Dr. Levin also established and supervised laboratories dedicated to the research of mechanisms of toxicity, biochemical toxicology and toxicokinetics.

PATRICIA LOWENSTAM
Vice President, Human Resources and Operations

Ms. Lowenstam has served as our Vice President, Human Resources since January 1995. She joined Isis in August 1992 as our Director, Human Resources and served in that capacity until January 1995. Prior to joining Isis, she held senior management positions in Human Resources with Quotron Systems, Inc., Citicorp, Zale Corporation, and the May Company.

KAREN LUNDSTEDT
Vice President, Investor Relations and Corporate Communications

Ms. Lundstedt has served as our Vice President, Investor Relations and Corporate Communications since April 2000. Ms. Lundstedt joined Isis in August 1999 as our Executive Director, Investor Relations and Corporate Communications. From September 1991 until joining Isis, Ms. Lundstedt held various management positions at Dura Pharmaceuticals, a specialty respiratory pharmaceutical and pulmonary drug delivery company.

JOHN MCNEIL
Vice President, Informatics

Mr. McNeil has served as our Vice President, Informatics since October 1999. Mr. McNeil joined Isis in October 1997 as our Director, Informatics. Prior to joining Isis, Mr. McNeil was President of

John McNeil & Co., Inc., and held various positions at SAIC in San Diego from 1989 to 1997, including Manager of the Laboratory Sensors and Automation division.

ARON F. STEIN, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance

Dr. Stein has served as our Vice President, Regulatory Affairs and Quality Assurance since August 2002. Prior to joining Isis, Dr. Stein was Divisional Vice President of Medical and Regulatory Affairs, Hospital Products Division for Abbott Laboratories from September 1999 to August 2002, and Vice President in charge of Regulatory Affairs and Quality Assurance for SEQUUS Pharmaceuticals, Inc. from April 1997 to September 1999.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this Form 10-K, 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.

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 these approvals 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 also could have a negative impact on our financial results.

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 that our partners or we can successfully commercialize these drug candidates.

If the results of clinical testing indicate that any of our drugs under development, including Affinitak and alicaforsen, are not suitable for commercial use, or if additional testing is required to demonstrate 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. We are applying most of our resources 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.

In March 2003, we reported the results of our Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer. In this trial, Affinitak, when added to carboplatin and paclitaxol, failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with the Affinitak trial Lilly is currently conducting as well as the trials for our other drugs. In 2004, we expect to report the results of our Phase III clinical trials of Alicaforsen in patients with active Crohn's disease. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

If the market does not accept our products, we are not likely to generate 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, if approved for commercialization, doctors will use our products 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. Our partners and we may not successfully commercialize 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 and effectiveness 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 cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

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;
- Conduct clinical trials; and
- Successfully commercialize existing and future product candidates.

If any of our partners fail to develop or sell any drug in which we have retained a financial interest, our business may suffer. 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. Examples of terminated collaborations include the termination in 2002 of our HepaSense and Orasense collaborations with Elan and the termination of our collaboration with Merck to develop ISIS 113715.

We are collaborating with Lilly to develop Affinitak, our most advanced drug candidate, with Lilly funding Affinitak's development. Lilly could decide to discontinue its funding of Affinitak at any time. The results of our recently completed Phase III clinical trial for Affinitak, the market potential of Affinitak or negative results from Lilly's Phase III clinical trial for Affinitak could influence Lilly's decision to discontinue funding of future Affinitak activities.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly. In addition, since its inception, Ibis has received significant financial support from various government agencies to use its technology to develop our sensor to identify infectious agents. We have received significant financial support from U.S. Government-funded grants and contracts for our Ibis program and the development of our TIGER biosensor. The U.S. Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical company or government partners stopped funding and/or developing these products, our business could suffer.

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

In addition, the disappointing results of our first Affinitak Phase III trial could cause our existing partners to reevaluate their commitment to our drug discovery platforms or could impair our ability to attract new collaborative partners. If any of our collaborative partners withdraw their resources or if we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

We have incurred losses, and our business will suffer if we fail to achieve profitability in the future.

Because drug discovery and development and research services require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of December 31, 2003, our accumulated losses were approximately $555.6 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. We currently derive our current product revenue 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.

We may not successfully develop or derive revenues from our business based on our TIGER biosensor to identify infectious organisms.

Our TIGER biosensor is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our biosensor due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our TIGER business could fail to meet our business and financial objectives.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All 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 as of December 31, 2003, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements for at least the next 36 months. If we do not meet our goals to commercialize our drug products and research services or to license 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 developing and commercializing a business based on our TIGER biosensor to identify infectious organisms; 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 we raise additional funds 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 have 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. We have limited experience manufacturing pharmaceutical products of the chemical class represented by

our drug candidates, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small 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 the FDA enforces 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 after approval that could limit the commercial success of our potential product.

If the results of our Phase III trials for alicaforsen are positive and we fail to secure a marketing and distribution partner for this product, our commercialization efforts for alicaforsen may be harmed or delayed.

We have limited personnel with experience in marketing, selling and distributing products. We expect to depend on third parties to commercialize alicaforsen if our Phase III trials for alicaforsen are positive and we receive marketing approval. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for alicaforsen. We may not successfully establish a collaboration or be able to make alternative arrangements. Moreover, a collaboration or other arrangement we secure may not succeed.

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 or unique methods of identifying infectious organisms. Our competitors may succeed in developing drug candidates or technologies that are more effective than any drug candidates or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

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 cannot protect our patents or our proprietary rights, others may compete more directly against us.

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents 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.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have 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 U.S. 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, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease. For example, since the data from our Phase III trial for Affinitak were not sufficiently positive to support a single study NDA, we now must wait for the results of Lilly's ongoing Phase III Affinitak trial before we reevaluate whether the data are sufficiently positive to support filing an NDA for Affinitak. We expect results from this second Phase III trial in the second half of 2004.

If Macugen does not achieve marketing approval or its commercial success does not meet our expectations, we will not receive milestone and royalty payments.

As part of our license agreement with Eyetech, we are entitled to receive milestones and royalty payments. However, if Eyetech does not achieve these milestones or receive marketing approval for Macugen, or if Eyetech receives marketing approval for Macugen but fails to commercialize Macugen as expected, we may not receive these payments, or derive the expected value.

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 executive officers. 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. Failure to succeed in specific clinical trials, including the results of our first Phase III Affinitak trial, may make it more challenging to recruit and retain qualified scientific personnel.

We depend on third parties in the conduct of our clinical trials for our product candidates and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of our clinical trials for our product candidates and expect to continue to do so in the future. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates.

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 our securities. During the 12 months preceding December 31, 2003, the market price of our common stock has ranged from $2.50 to $8.05 per share. Many factors can affect the market price of our securities, 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 ?% 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, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. 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, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock which are currently outstanding and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these holders exercise their registration rights, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

Item 2. Properties.

As of March 3, 2004, we occupied approximately 218,000 square feet of laboratory and office space, including 6,888 square feet of manufacturing area built to meet Good Manufacturing Practices. We are primarily located in six buildings in Carlsbad, California. We own three of these buildings and, as of December 31, 2003, these buildings secured approximately $6.4 million of our debt. We lease three of the buildings under lease agreements, of which two leases will expire in 2007 and one will expire in 2010. In February 2003, we completed an expansion of our manufacturing facility to upgrade our existing manufacturing suite and add a second state of the art manufacturing suite.

Item 3. Legal Proceedings.

We are not a party to any material legal proceedings.

Item 4. Submission of Matters to a Vote of Security Holders.

Not applicable.

PART II

Item 5. Market For Registrant's Common Equity and Related Stockholder Matters.

Our common stock is traded publicly through the Nasdaq National Market under the symbol "ISIS." 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.

	HIGH	LOW
2003		
First Quarter	$ 7.55	$ 2.50
Second Quarter	$ 6.85	$ 3.50
Third Quarter	$ 8.05	$ 4.55
Fourth Quarter	$ 7.07	$ 5.20
2002		
First Quarter	$ 22.40	$ 14.07
Second Quarter	$ 18.00	$ 6.76
Third Quarter	$ 11.86	$ 6.10
Fourth Quarter	$ 11.00	$ 6.00

As of March 3, 2004, there were approximately 1,084 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Recent Sales of Unregistered Securities

Not applicable.

Purchases of Equity Securities by Us and Affiliated Persons

Not applicable.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2003.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders	3,013,000(a)	$ 9.90	3,251,000(c)
Equity compensation plans not approved by stockholders	5,198,000(b)	$ 7.94	539,000
Total	8,211,000	$ 8.66	3,790,000

(a) Consists of two Isis plans: 1989 Stock Option Plan and the 2002 Non-Employee Directors' Stock Option Plan.

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below.

(c) Of these shares, 200,138 remain available for purchase under the 2000 Employee Stock Purchase Plan. The 2000 Employee Stock Purchase Plan incorporates an evergreen formula pursuant to

which on each January 1 for the first 9 anniversaries, we automatically increase the aggregate number of shares reserved for issuance under the plan by the lesser of (i) 1% of the total number of shares of Common Stock outstanding on such anniversary date or (ii) 200,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of nonstatutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2003, the 2000 Plan had 5,737,000 shares reserved for issuance, options to purchase an aggregate of 5,198,000 shares have been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 253,000 shares have been exercised under the 2000 Plan, and 539,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the optionee's employment or service as a consultant or term as an affiliate. Options granted pursuant to the April 2003 stock option exchange program as discussed in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," and in the Notes to Consolidated Financial Statements, expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the optionee's employment or service as a consultant or term as an affiliate.

If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

-

a sale, lease or other disposition of all or substantially all of our assets;

- a merger or consolidation in which we are not the surviving corporation; or

- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise.

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. In addition, as of December 31, 2003, approximately 5,198,000 stock awards granted under the 2000 plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

Available Information

We make available on our web site, *www.isispharm.com*, our 10-K, 10-Q's, 8-K's and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that is included on or linked to our Internet site is not a part of this report or any registration statement that incorporates this report by reference.

Item 6. Selected Consolidated Financial Data (in thousands, except per share amounts):

	Years Ended December 31,				
	2003	2002	2001	2000	1999
Consolidated Statement of Operations Data:					
Revenue (includes amounts for R&D, licensing and royalties)	$ 49,990	$ 80,179	$ 53,273	$ 37,255	$ 33,925
Research and development expenses	$ 116,963	$ 124,074	$ 83,741	$ 57,014	$ 66,413
Net loss applicable to common stock	$ (95,690)	$ (73,302)	$ (75,131)	$ (54,699)	$ (59,645)
Basic and diluted net loss per share	$ (1.73)	$ (1.35)	$ (1.70)	$ (1.48)	$ (2.08)
Shares used in computing basic and diluted net loss per share	55,463	54,480	44,109	37,023	28,703

	Years Ended December 31,				
	2003	2002	2001	2000	1999
Consolidated Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 215,504	$ 289,353	$ 312,018	$ 127,262	$ 52,839
Working capital	$ 194,004	$ 244,230	$ 280,569	$ 118,568	$ 44,213
Total assets	$ 334,942	$ 438,683	$ 417,061	$ 183,256	$ 103,107
Long-term debt and capital lease obligations, less current portion	$ 213,397	$ 192,893	$ 125,710	$ 102,254	$ 87,254
Accumulated deficit	$ (555,583)	$ (459,893)	$ (386,591)	$ (311,460)	$ (256,761)
Stockholders' equity	$ 67,178	$ 155,477	$ 223,099	$ 66,366	$ 869

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into 11 antisense drugs currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including inflammatory, viral, metabolic, dermatological and cardiovascular diseases, and cancer. We are studying these drugs in intravenous, subcutaneous, topical cream, enema, aerosol, and oral formulations, and we are advancing antisense drugs using second-generation chemistry. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen) in 1998.

Affinitak, formerly LY900003 or ISIS 3521, which we licensed to Eli Lilly and Company, or Lilly, in 2001, is our most advanced product in development. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single study new drug application. Lilly and we completed an analysis of the data from this trial and presented a summary of the findings at the 39th Annual Meeting of the American Society of Clinical Oncology in June 2003. In a second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which most likely will occur in the second half of 2004.

We are conducting two Phase III clinical trials for another product, ISIS 2302, or alicaforsen, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America and Europe. We expect to report data from these clinical trials in the second half of 2004. We also have Phase

II programs ongoing for five additional products.

Our Ibis program has invented a platform technology that has the potential to revolutionize the identification of infectious diseases. Through a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we have applied our proprietary technologies to develop a biological sensor to identify a broad range of infectious organisms in a sample, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. To date, our Ibis program has received awards and contracts of up to $55.0 million from agencies of the U.S. Government, including DARPA, CDC, USAMRIID, the United States Navy, and the FBI, among others.

We have a broad patent portfolio covering our technologies. We have rights to more than 1,300 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 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, through licenses we grant them. Licensing partnerships may include antisense drug discovery collaborations like those we have with Lilly and Amgen, functional genomics agreements, like our licenses to Chiron, Amgen, Sequitur and atugen AG. We also license our non-antisense patents, as we did to Eyetech Pharmaceuticals, Inc, or Eyetech. To date, we have generated more than $35.0 million in license and royalty fees related to our patent portfolio.

We are pursuing three early-stage antisense mechanisms, including RNA Interference, or RNAi, micro-RNA, and alternative splicing through research collaborations and partnerships.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of propriety of revenue recognition and associated deferred revenue;
- Determination of proper valuation of investments in marketable securities;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of proper valuation of inventory;
- Determination of appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimation of our net deferred income tax asset valuation allowance.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include Staff Accounting Bulletin No. 101, or SAB 101, *"Revenue Recognition in Financial Statements,"* SAB 104, *"Revenue Recognition,"* and Financial Accounting Standards Board Emerging Issue Task Force No. 00-21, or EITF 00-21, "*Accounting for Revenue Arrangements with Multiple Deliverables*."

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. We include in deferred revenue on the balance sheet any revenues which we are entitled to bill or have collected in advance of recognizing the associated revenue.

We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. We recognize revenue related to up-front payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Amgen, Chiron, ITRI, Lilly and the Singapore EDB.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the research collaboration. We take quarterly drawdowns against this loan and discount the amounts to

their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. As of December 31, 2003, we had drawn down $73.8 million on this loan. We are accreting the loan up to its face value over its term by recording interest expense. The

difference between the cash received and the present value of the loan represents value Lilly gave to us to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestones upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable, and we are not obligated to future performance related to the achievement of the milestone. We recognized revenue during 2003 related to milestones achieved under our agreements with Lilly, Amgen, and ITRI.

We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. To date, in two instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that our obligation was complete under the terms of the manufacturing agreement in place, and title had transferred to the customer, before we recognized the related revenue.

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

We sometimes enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element, and we are reasonably assured of collecting the resulting receivable.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, "*Accounting for Certain Investments in Debt and Equity Securities."* We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in cash and cash equivalents, we also have equity investments in privately-and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost is other-than-temporary in our equity positions, we examine historical trends in the stock price, the financial condition, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the first quarter of 2003, we recorded a non-cash loss of $2.4 million related to the impairment of our equity investments in ATL and Hybridon. We recorded these charges based on declines in market value of the equity investments, as compared to their initial valuations, which we determined to be other-than-temporary.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment

listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;
- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and
- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents

In the event that we determine that impairment exists where we had previously determined that it did not exist, we may need to make a material adjustment to our consolidated financial statements. To date, we have experienced no significant impairment of our long-lived assets.

Valuation of Inventory

We include in inventory material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak to zero.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Asset

As disclosed in Note 5 of Notes to the Consolidated Financial Statements, we record net deferred tax assets. We record a valuation allowance to offset the net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future

taxable income and record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset. As of December 31, 2003, our deferred tax assets and valuation allowance totaled approximately $235.0 million.

Results of Operations

Years Ended December 31, 2003 and December 31, 2002

Revenue

Total revenue for the year ended December 31, 2003 was $50.0 million, compared to $80.2 million for 2002. The decrease of $30.2 million was primarily due to the reduction in revenue associated with the clinical development of Affinitak and the conclusion of Elan's participation in the Orasense and HepaSense collaborations in late 2002. We did not have revenue associated with Orasense and HepaSense in 2003 as a result of the conclusion of Elan's participation in the joint ventures. New revenue sources not present in 2002 offset, in part, the decreases in total revenue in 2003.

Research and Development Revenue under Collaborative Agreements

Under the category research and development revenue under collaborative agreements, for the year ended December 31, 2003, we earned $49.5 million, compared to $67.8 million for 2002. The decrease of $18.3 million was primarily due to the reduction in revenue associated with the clinical development of Affinitak. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single- study new drug application. New sources of revenue not present in 2002 slightly offset the previously described decreases in revenue. New sources of revenue from our Antisense Drug Discovery collaborations included:

- an upfront fee and milestone payments from ITRI;
- a milestone achieved in the development of LY2181308, the antisense inhibitor of survivin, as part of our research collaboration oncology expansion with Lilly;
- a milestone achieved in our drug discovery collaboration with Amgen; and
- an upfront fee from the expansion of our antisense drug development partnership with OncoGenex.

New revenue sources from our Ibis program resulted from the expansion of work to continue the advancement of our TIGER technology, which included work for government agencies such as the CDC, FBI, and DARPA. Our work for DARPA continues to be a collaborative effort with SAIC and accounted for approximately 16% and 6% of our revenue in 2003 and 2002, respectively. Our ability to maintain revenue at current levels will depend on new revenue sources and expansion of existing revenue sources in 2004.

Research and Development Revenue from Affiliates

Research and development revenue from affiliates consisted of revenue associated with our two collaborations with Elan, Orasense and HepaSense. Elan concluded its participation in the HepaSense and Orasense collaborations in late 2002, in conjunction with its restructuring efforts. As a result, we reacquired product rights to ISIS 14803 for hepatitis C and the oral formulation of ISIS 104838 from the HepaSense and Orasense joint ventures, respectively. We did not earn revenue from these affiliates in 2003. During 2002, we recognized $8.9 million and $3.0 million as revenue from Orasense and HepaSense, respectively. We do not expect to earn revenue related to these collaborations in 2004.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $523,000 for the year ended December 31, 2003, compared with $417,000 in 2002. We do not anticipate that revenue from licensing activities and royalties will comprise a significant portion of our revenue in 2004.

Operating Expenses

Total operating expenses were $129.0 million and $131.0 million for the years ended December 31, 2003 and 2002, respectively. The decrease of $2.0 million was primarily due to our implementation of an expense reduction plan during the second quarter of 2003, the completion of our development activities for Affinitak, and the termination of our Genetrove database product offering in November 2002. Increased clinical development expenses for many of our other products and increased costs in the Ibis program partially offset the decrease in operating expenses. Increased expenses of $3.9 million and $430,000 for

compensation related to stock options and restructuring activities, respectively, further offset the decrease in operating expenses. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation expense or benefit related to stock options from operating expenses because it is based on the variability of our stock price rather than operations. We also believe that it is important to exclude restructuring activities because these costs are directly related to isolated events.

Research and Development Expenses

For the year ended December 31, 2003, we reported total research and development expenditures of $117.0 million, compared to $124.1 million reported in 2002. Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis program and related R&D Support costs. The antisense drug discovery costs include costs associated with our GeneTrove program. The decrease of $7.1 million in 2003 over 2002 was primarily due to the termination of our GeneTrove product offering and reorganization of the GeneTrove program in November 2002, our implementation of an expense reduction plan in April 2003, and a decrease in our total Affinitak related expenses. Increased clinical development expenses for many of our other products and our increased efforts in the Ibis program offset, in part, our decreases in research and development expenditures. We expect that total research and development spending will increase in 2004 to support our ongoing research and development activities.

Antisense Drug Discovery

Identifying what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process for our researchers. We use this information in our internal drug discovery process and, through our GeneTrove program, we sell these services and the resulting information to pharmaceutical and biotechnology companies in collaborations. GeneTrove is an integral component of our antisense drug discovery group. As such, GeneTrove shares many of its resources including people, equipment and facilities with the rest of our antisense drug discovery group. In November 2002, we terminated our GeneTrove database product offering and reorganized the GeneTrove program. We incurred a one-time charge of approximately $1.4 million associated with this restructuring in the fourth quarter of 2002. The cost savings from the termination of our GeneTrove database has been offset, in part, by increases in gene functionalization and target validation services for our in-house drug discovery programs and our existing partners. Our current focus is to use GeneTrove information to direct our own drug discovery research and that of our antisense drug discovery partners, like Lilly and Amgen. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology. Through the efforts of our scientists in the antisense drug discovery group, we have produced second-generation antisense drugs that have been shown to have increased potency, increased stability, an improved side effect profile and the potential for oral administration. With more

than a decade focused on learning the capabilities of antisense technology and how these compounds behave in the body, our scientists have learned the organs and tissues in humans to which antisense therapy is effectively directed. Using this knowledge, we have strategically focused our research programs on those sites in the body that accept antisense readily like the liver, kidney, fat tissue and bone marrow. These targets expand the current therapeutic scope of antisense research into new disease categories, including obesity and cardiovascular disease. The work of our scientists has given us the opportunity to enter into important drug discovery relationships with industry leaders like Lilly and Amgen.

As we expand our research programs into new sites in the body and new disease categories, we would expect to see our expenses for antisense drug discovery increase. We anticipate that our existing relationships with Lilly and Amgen combined with our collaborations with ITRI, the Singapore EDB and Ercole and prospective new partners, will continue to help fund our many research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug discovery costs for the year ended December 31, 2003 totaled $36.8 million compared to $38.9 million for 2002. The decrease of $2.1 million in 2003 over 2002 was principally a result of our planned expense reductions started in the second quarter of 2003 and the termination of our GeneTrove database product offering and reorganization of the GeneTrove program in November 2002. These decreases were offset in part by the increase in expenses to support our research collaborations with Lilly, Amgen, and ITRI.

Antisense Drug Development

Our development activities reflect our efforts to advance our drugs through the various stages of preclinical, or animal studies, and human clinical trials. The development plans for our drugs are subject to numerous uncertainties like obtaining regulatory approval, market availability and successfully obtaining funding, which may affect our research and development expenditures and capital resources. Prior to starting clinical trials, we test our potential product candidates in numerous preclinical studies to identify disease indications for which they may be candidates. Once we have established that a preclinical drug candidate has met certain clinical requirements and we have filed an Investigational New Drug Application, or IND, with the FDA, we may initiate clinical trials for that drug. It may take several years to complete clinical trials, with the length varying substantially according to the complexity, novelty and intended use of the product candidate. The following timelines represent our estimate of typical completion times for clinical trials we generally conduct: Phase I—one year, Phase II—one to two years, and Phase III—two to four years. However, the duration and the cost of clinical trials may vary significantly depending on a variety of factors including a trial's protocol, the number of patients in the trial, the duration of patient follow-up, the number of clinical sites in the trial, and the length of time required to enroll suitable patient subjects. Although we spend a considerable amount of time planning our clinical trials, often we are required to alter from our plan. For example, we may need to alter the number of patients in a trial or extend the duration of patient follow-up. Any required deviation from our plan may require us to incur additional expenditures.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the variety of indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Generally, a late stage Phase III trial is substantially more expensive than early stage trials, such as Phase I or Phase II. Currently we have 11 drug candidates in various stages of development, including two drugs in Phase III clinical trials. In March 2003, we announced the results of our Phase III clinical trial of Affinitak for the treatment of non-small cell lung cancer. The results were not sufficient to support a single study new drug application. In a second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which most likely will occur in the second half of 2004. Affinitak related

expenses decreased in 2003 compared to 2002. We have two Phase III trials of alicaforsen, or ISIS 2302, in people with active Crohn's disease. We are conducting one of these studies in North America and the other in Europe. These studies are evaluating the safety and efficacy of alicaforsen. We also have Phase II programs ongoing for five additional products, Phase I programs ongoing for three additional products, and preclinical studies ongoing for one project. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. For example, under our licensing agreement with Lilly for Affinitak, we received an upfront license payment that helped fund the costs we incurred during 2001 for our Phase III trial. In addition, during 2002 and 2003, Lilly reimbursed us for our costs related to our development of Affinitak.

Development expenditures totaled $45.1 million and $55.3 million for the years ended December 31, 2003 and 2002, respectively. The decrease of $10.2 million was primarily due to planned expense reductions started in the second quarter of 2003 driven by a reduction in clinical development activity related to Affinitak. These decreases were offset, in part, by increased clinical development expenses for our other products, mainly alicaforsen for Crohn's disease and several products in Phase II and earlier stages of development.

The planned expense reductions began in April 2003 when we initiated a restructuring effort in response to the disappointing results from our Phase III trial of Affinitak. As a result, we had a small reduction in our workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. We completed our development activities for Affinitak in 2003. As a result, expenditures related to Affinitak decreased from $22.6 million in 2002 to $5.1 million in 2003. The majority of the 2003 expenditures occurred in the first quarter of 2003.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $6.5 million for the year ended December 31, 2003, compared to $4.8 million for the same period of 2002. The increase of $1.7 million was the result of an increase in the number of patients undergoing treatment in our two Phase III trials. These trials were initiated in November 2001 and June 2002.

Expenditures related to our other products in development totaled $29.3 million for the year ended December 31, 2003, compared to $23.1 million for 2002. The increase of $6.2 million in 2003 over 2002 was mainly the result of increased expenses for Phase II trials of alicaforsen in ulcerative colitis, the Phase I trials for ISIS 113715 for type 2 diabetes and preclinical studies and initiation of a Phase I trial of ISIS 301012 for cardiovascular disease.

Ibis

Expenditures in our Ibis program have historically included costs for scientists, equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of anti-infectives. Costs for these items have increased since Ibis expanded the application of its technology to develop a biosensor to identify a broad range of infectious organisms in a sample, including organisms that are, newly-emerging, genetically altered, or unculturable.

Since its inception, Ibis has received significant financial support from various government agencies to advance its technology for the identification and treatment of infectious disease. From June 2000 through June 2002, Ibis also received funding from its collaboration with Pfizer, which ended in June 2002 in accordance with the terms of the agreement.

Ibis expenditures for the year ended December 31, 2003 totaled $9.9 million, compared to $8.3 million for 2002. The increase of $1.6 million was primarily related to Ibis' continued performance obligations under its multi-year government contracts with DARPA through our relationship with SAIC, awarded in October 2001, and USAMRIID, awarded in March 2002, and new performance obligations under Ibis' agreement with the CDC, awarded in September 2003, and with various other government agencies. Included as Ibis expenditures are fixtures and equipment accounted for as pass-through costs

that Ibis purchased for government agencies under the contractual terms of their agreements. We expect our costs for Ibis to increase as we continue to expand this business.

R&D Support

In our research and development expenses, we include support costs such as rent, building and equipment repair and maintenance, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D Support costs. Generally these costs represent approximately 17% to 22% of our total annual research and development expenses.

R&D Support costs for the year ended December 31, 2003 totaled $25.2 million, compared to $21.6 million for 2002. The increase of $3.6 million was primarily due to increases in our research and development efforts related to our efforts to prepare for the manufacture and commercialization of Affinitak in the first quarter of 2003, our increased efforts related to our government contracts and increased depreciation resulting from the completion of laboratory build-outs. Our planned expense reductions initiated in April 2003 offset, in part, the increases in our research and development efforts noted above.

General and Administrative Expenses

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of business development, legal, human resources, investor relations and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

General and administrative expenses for the year ended December 31, 2003 totaled $9.3 million compared to $8.5 million for 2002. This $800,000 increase was primarily a result of an increase in employees and related benefits in the first quarter of 2003. A reduction in the number of employees and a corresponding reduction in expense as a result of the restructuring in April 2003 offset, in part, the increases noted above. We expect general and administrative expenses to increase in 2004 to support our ongoing R&D activities.

Compensation Related to Stock Options

Compensation expense for the year ended December 31, 2003 was $913,000, compared to compensation benefit of $3.0 million for the year ended December 31, 2002. Compensation expense for 2003 primarily consisted of expense for stock options associated with the employee stock option exchange

program we initiated in April 2003. We accounted for options affected by the 2003 option exchange program as variable stock options in accordance with Accounting Principles Board Opinion No. 25, or APB 25, and Financial Accounting Standards Board Interpretation No. 44, or FIN 44. APB 25 and FIN 44 required us to account for these exchange options as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. We also recorded nominal expense in 2003 related to stock options granted in prior years to consultants, and we accounted for these options in accordance with Emerging Issues Task Force Abstract No. 96-18, or EITF 96-18. The compensation benefit in 2002 represented the reversal of previously recorded compensation expense for stock options accounted for as variable stock options associated with the option exchange program we offered to non-officer employees in January 2000. At December 31, 2002, either employees exercised or we had cancelled all of the variable stock options associated with the 2000 option exchange program.

Restructuring Activities

In April 2003, we initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, we had a small reduction in our workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, we incurred a restructuring charge of $1.8 million during the second quarter of 2003. Isis completed the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

In November 2002, we announced the termination of our GeneTrove database product offering and the reorganization of our GeneTrove program. As a result, we reduced our workforce by approximately 25 people. The restructuring plan included the write-down of certain intellectual property valued at $605,000. As a result of this plan, we incurred a one-time charge of $1.4 million for restructuring activities in the fourth quarter of 2002. We did not recognize any additional GeneTrove restructuring related charges for the year ended December 31, 2003, and completed utilization of the reserve related to the GeneTrove restructuring in the fourth quarter of 2003.

Equity in Loss of Affiliates

In late 2002, Elan concluded its participation in the Orasense and HepaSense collaborations in conjunction with its restructuring efforts. As a result, we regained all rights to ISIS 104838, the compound that Elan and we were developing within Orasense. We continue to develop certain of our oral delivery technology within Orasense. We also regained all rights to ISIS 14803, the compound that Elan and we were developing within HepaSense.

We did not have equity in loss of affiliates for the year ended December 31, 2003. As mentioned previously, we used the equity method of accounting for our investments in Orasense and HepaSense in 2002. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense as equity in loss of affiliates during 2002. Our equity in loss of affiliates for the year ended December 31, 2002 consisted of $9.5 million for Orasense and $6.5 million for HepaSense.

Investment Income

Investment income for the years ended December 31, 2003 and 2002 was $5.1 million and $8.5 million, respectively. The $3.4 million decrease in investment income in 2003 compared to 2002 was primarily due to our lower cash, cash equivalents and short-term investments balances in 2003 compared to 2002, and a decline in interest rates as a result of then current market conditions.

Interest Expense

Interest expense for the year ended December 31, 2003 was $18.7 million compared to $16.6 million for the same period in 2002. The $2.1 million increase in interest expense in 2003 compared to 2002 was primarily due to a higher average debt balance during 2003 than during 2002. The increase in debt compared to 2002 related primarily to additional drawdowns under our debt agreement with Lilly. A decrease in the average interest rate on our debt offset, in part, the effect of a higher average debt balance. The decrease in the average debt interest rate was primarily due to the retirement in May 2002 and July 2002 of higher interest rate debt with proceeds from the issuance, in May 2002, of our $5^{1}/_{2}$% convertible notes due in 2009 and to the retirement, in the fourth quarter of 2003, of higher interest rate debt with proceeds from our $32.0 million term loan from Silicon Valley Bank secured in December 2003. The debt retired in the fourth quarter of 2003 consisted of convertible partner debt that carried interest rates ranging from 8.5% to 12%. The new term loan bears interest at the prime

rate, which was 4.0% at December 31, 2003. We can convert the interest rate to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%.

In 2003, $7.5 million of the $18.7 million in interest expense did not require cash payment. This represents the accrual of interest expense related to the $100.0 million loan Lilly has made available to us to fund the research collaboration.

Loss on Prepayment of 14% Notes

For the year ended December 31, 2002, we reported a $2.3 million loss on prepayment of debt, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest, on the prepayment of approximately $74.0 million of our 14% Senior Subordinated Notes. No such prepayment occurred in 2003.

Gain on Prepayment of 12% Notes

In July 2002, we used $14.7 million in cash to prepay $19.7 million of 12% convertible debt Elan held. As a result, we reported a $5.0 million gain on prepayment of debt for the year ended December 31, 2002. No such prepayment occurred in 2003.

Net Loss Applicable to Common Stock

For the years ended December 31, 2003 and 2002, we reported a net loss of $95.0 million and $72.2 million, respectively. Our net loss applicable to common stock was $95.7 million for the year ended December 31, 2003, and $73.3 million for 2002, included $694,000 and $1.1 million, respectively, of accreted

dividends on preferred stock. The decrease in accreted dividends in 2003 from 2002 was the result of the August 2002 conversion of 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of our common stock using a conversion price of $12.54 per share. Included in the conversion was approximately $2.1 million in preferred stock dividends accrued in prior years. The increase in the net loss applicable to common stock was primarily a result of the increase in loss from operations, a non-cash loss on investments of $2.4 million related to the other-than-temporary impairment of our investments in ATL and Hybridon and the absence of a net gain on debt extinguishment recorded in 2002.

Net Operating Loss Carryforward

At December 31, 2003, our net operating loss carryforward for federal income tax purposes was approximately $312.1 million. The net operating loss, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets. We will use the net operating loss and research credits, and realize the benefit of these deferred tax assets, if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our research credit carryforward and capitalized research expense for federal income tax purposes was approximately $21.9 million and $57.0 million, respectively, as of December 31, 2003. Our federal net operating loss and research credit carryforwards will begin expiring in 2007 and 2004, respectively, unless previously utilized. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods, due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Years Ended December 31, 2002 and December 31, 2001

Revenue

Total revenue for the year ended December 31, 2002 was $80.2 million, compared to $53.3 million for 2001. The increase of $26.9 million was primarily a result of increased research and development revenue under collaborative agreements. The most significant contributor was our strategic alliance with Lilly. A decrease in revenue from licensing and royalty revenue in 2002 from that reported in 2001 partially offset the increase in total revenue.

Research and Development Revenue under Collaborative Agreements

Under the category research and development revenue under collaborative agreements, for the year ended December 31, 2002, we earned $67.8 million, compared to $40.4 million for 2001. The increase of $27.4 million was a result of several collaborations in place during 2002 which were in effect for only a part of 2001 or not in place during 2001. Our Lilly alliance, which we entered into in August 2001, significantly contributed to the increase in 2002 over 2001. Other sources of revenue present in 2002 but only in part or not at all in 2001 included certain GeneTrove agreements and our Ibis biological warfare defense research programs with DARPA and USAMRIID. In addition, during 2002 we earned a milestone under each of our antisense drug discovery collaborations with Amgen and Merck. The June 2002 termination of our Ibis collaboration with Pfizer and a related decrease in earned milestones in 2002 compared to 2001 partially offset the increase in research and development revenue under collaborative agreements.

Research and Development Revenue from Affiliates

Research and development revenue from affiliates consisted of revenue associated with our two collaborations with Elan, Orasense and HepaSense. Elan concluded its participation in the HepaSense and Orasense collaborations in late 2002, in conjunction with its restructuring efforts. During 2002, we recognized $8.9 million and $3.0 million from Orasense and HepaSense, respectively, as revenue. During 2001, we recognized $5.4 million and $5.2 million as revenue from Orasense and HepaSense, respectively. The increase in revenue from the Orasense collaboration was primarily due to the progression of ISIS 104838 into later stages of clinical development. The decrease in revenue from the HepaSense collaboration was primarily due to the conclusion of the collaboration during the second half of 2002.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $417,000 for the year ended December 31, 2002, compared with $2.3 million in 2001. The decrease of $1.9 million was primarily related to one-time revenue recorded in 2001 associated with a $2.0 million license fee paid to us by Eyetech Pharmaceuticals, Inc., a publicly traded company.

Operating Expenses

Total operating expenses were $131.0 million and $99.4 million for the years ended December 31, 2002 and 2001, respectively. The increase of $31.6 million was primarily due to a $40.3 million increase in research and development activities to support the various products we had in development during 2002, and our research collaborations with Lilly and Amgen. In addition, we had $1.4 million in expenses related to restructuring activities during 2002. A decrease of $2.5 million in general and administrative expenses, and a $7.6 million decrease in compensation related to stock options, offset the increase in operating expenses.

Research and Development Expenses

For the year ended December 31, 2002, we reported total research and development expenditures of $124.1 million, compared to $83.7 million reported in 2001. The $40.4 million increase in 2002 over 2001 was primarily due to our investment in the various products we had in development during 2002, including three Phase III clinical trials, costs associated with our Lilly and Amgen research collaborations, and costs associated with increased gene functionalization and target validation activities in support of our numerous GeneTrove collaborations.

Our research and development expenses consisted of costs for antisense drug discovery, including GeneTrove, antisense drug development, our Ibis program and related R&D Support costs.

Antisense Drug Discovery

Antisense drug discovery costs for the year ended December 31, 2002 totaled $38.9 million compared to $20.9 million for 2001. The increase was principally a result of a full year's activity related to the Lilly research collaboration, the September 2002 expansion of the Lilly research collaboration to include oncology, and the advancement of research related to our Amgen research collaboration.

Antisense Drug Development

Development expenditures totaled $55.3 million and $37.9 million for the years ended December 31, 2002 and 2001, respectively. The increase of $17.4 million reflected the expansion and advancement of our pipeline. During 2002, we had 13 products in development including two products, Affinitak and alicaforsen for Crohn's disease, in Phase III clinical trials and six products in Phase II clinical trials. Expenditures related to Affinitak in 2002 totaled $22.6 million, compared to $11.5 million in 2001. The increase of $11.1 million in 2002 over 2001 was a result of delivery of Affinitak drug to Lilly for use in clinical trials, expenses for our Phase III trial of Affinitak and the advancement of our various Phase II trials for Affinitak.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $4.8 million for the year ended December 31, 2002, compared to $3.4 million for the same period of 2001. The increase of $1.4 million for the year ended December 31, 2002 over the same period in 2001 was a result of our two Phase III trials initiated in November 2001 and June 2002, in the United States and Europe, respectively.

Expenditures related to our other products in development totaled $23.1 million in 2002 compared to $16.2 million in 2001. The increase of $6.9 million in 2002 over 2001 was a result of the development of the other antisense products in our pipeline, including expenses related to the initiation of our Phase II clinical trials for alicaforsen in ulcerative colitis, ISIS 14803 and ISIS 104838 in 2002.

Ibis

Ibis expenditures for the year ended December 31, 2002 totaled $8.3 million, compared to $6.5 million in 2001. The increase of $1.8 million was primarily related to Ibis' performance obligations under its multi-year government contracts with DARPA, awarded in October 2001, and USAMRIID, awarded in March 2002.

R&D Support

R&D Support costs for fiscal year 2002 totaled $21.6 million, compared to $18.4 million for 2001. The increase of $3.2 million was a direct result of increases in our research and development efforts. While we work to control R&D Support costs, we expect that they will increase as direct research and development costs increase.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2002 totaled $8.5 million, compared to $11.1 million for the same period of 2001. This $2.6 million decrease was the result of certain costs previously included in general and administrative expenses, which we determined more accurately reflected research and development efforts.

Compensation Related to Stock Options

In 2002, we reversed $3.0 million of expense previously recorded in 2001 related to variable stock options. For the year ended December 31, 2001, we reported $4.6 million as compensation expense related to stock options. The compensation related to stock options was primarily a result of an option exchange program we offered to non-officer employees in January 2000. Accounting Principles Board Opinion No. 25 and Financial Accounting Standard Board Interpretation No. 44 required us to account for these exchange options as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. The decrease of $7.6 million in 2002 over 2001 was primarily a result of the 70% decrease in the price of our common stock as of December 31, 2002 compared to its price at December 31, 2001. In addition, we account for stock options granted to consultants in accordance with EITF 96-18, which contributed nominally to the expense recorded in 2002 and 2001. At December 31, 2002, either employees exercised or we cancelled all of the options associated with the 2000 option exchange program.

Restructuring Activities

In November 2002, we announced the termination of the GeneTrove database product offering and the reorganization of the GeneTrove program. As a result, we reduced our workforce by approximately 25 people. The restructuring plan included the write-down of certain intellectual property valued at $597,000. As of December 31, 2002, we incurred a charge of $1.4 million for restructuring activities. There were no restructuring charges in 2001.

Equity in Loss of Affiliates

Equity in loss of affiliates for the year ended December 31, 2002 was $16.0 million compared to $18.8 million for the year ended December 31, 2001. As mentioned previously, we used the equity method of accounting for our investments in Orasense and HepaSense. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense as equity in loss of affiliates. As of December 31, 2002, our equity in loss of affiliates from Orasense and HepaSense totaled $9.5 million and $6.5 million, respectively. In comparison, our equity in loss of affiliates as of December 31, 2001 was $10.3 million for Orasense and $8.3 million for HepaSense.

Investment Income

For the years ended December 31, 2002 and 2001, investment income was $8.5 million and $6.4 million, respectively. Although our ending cash balance decreased slightly in 2002 compared to 2001, our average cash balance was significantly higher, which favorably affected our investment income. In addition, in 2001 we realized a loss in an equity investment of approximately $515,000, which reduced our investment income for 2001.

Interest Expense

Interest expense for the year ended December 31, 2002 was $16.6 million compared to $15.2 million for the same period in 2001. Interest expense increased by $1.4 million in 2002 over 2001, primarily as a result of interest accrued on the May 1, 2002 issuance of $125.0 million of 5% convertible subordinated notes

and increased borrowings under the $100.0 million loan that Lilly made available to us to fund the research collaboration. The reduction in interest expense from the prepayment in May 2002 of our 14% Senior Subordinated Notes and the prepayment in July 2002 of a

portion of our Elan convertible notes for Orasense and HepaSense offset the aforementioned increases in interest expense.

In 2002, $8.6 million of the $16.6 million in interest expense, which was accrued under various long-term debt agreements, did not require cash payments. The long-term debt agreements with deferred interest and principal payments included our $100.0 million loan from Lilly and the remaining portion of our Elan line of credit for Orasense.

Loss on Prepayment of 14% Notes

For the year ended December 31, 2002, we reported a $2.3 million loss on prepayment of debt, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest, on the prepayment of approximately $74.0 million of our 14% Senior Subordinated Notes. We recorded the loss in the second quarter of 2002. No such loss occurred in 2001.

Gain on Prepayment of 12% Notes

In July 2002, we used $14.7 million in cash to prepay $19.7 million of 12% convertible debt Elan held. As a result, we reported a $5.0 million gain on prepayment of debt for the year ended December 31, 2002. We recorded the gain in the third quarter of 2002. No such gain occurred in 2001.

Net Loss Applicable to Common Stock

For the year ended December 31, 2002 and 2001, we reported a net loss of $72.2 million and $73.8 million, respectively. Our net loss applicable to common stock was $73.3 million for the year ended December 31, 2002, and $75.1 million in 2001, and included $1.1 million and $1.3 million of accreted dividends on preferred stock as of December 31, 2002 and 2001, respectively. The decrease in accreted dividends in 2002 from 2001 was the result of the August 2002 conversion of 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of our common stock using a conversion price of $12.54 per share. We included approximately $2.1 million in preferred stock dividends accrued in prior years in the conversion.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through December 31, 2003, we have approximately $400.5 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $589.1 million from the sale of equity securities. We have borrowed approximately $357.6 million under long-term debt arrangements to finance a portion of our operations of which $250.6 million remains outstanding at December 31, 2003.

At December 31, 2003, we had cash, cash equivalents and short-term investments of $215.5 million and working capital of $194.0 million. In comparison, we had cash, cash equivalents and short-term investments of $289.4 million and working capital of $244.2 million as of December 31, 2002. The decrease in our cash, cash equivalents and short-term investments, and working capital was primarily due to cash used to fund operating activities, capital purchases, additions to our patent portfolio, and repayment of $25.6 million in debt, including principal and accrued interest, to Elan, Abbott Laboratories, and Boehringer Ingleheim International BmbH, or BI, for $8.1 million, $1.0 million, and $16.5 million, respectively. Drawdowns in 2003 totaling $26.3 million from the $100.0 million loan provided by Lilly to fund our joint research collaboration, combined with net proceeds received from a $32.0 million term loan we secured from Silicon Valley Bank in December 2003 partially offset the decrease in cash. We expect that during 2004, we will finance our operations primarily from payments

generated from collaborative agreements and $21.3 million in drawdowns on the $100.0 million interest-free loan Lilly made available to us to fund our joint research collaboration.

As of December 31, 2003, our debt and other obligations totaled $250.6 million, compared to $233.8 million at December 31, 2002. Our debt and other obligations include current and long-term deferred contract revenue and contractual obligations that represent our payment obligations. The increase in our debt and other obligations was primarily due to additional draw downs from the $100.0 million interest-free loan from Lilly, which we discount to their present value by imputing interest on the amount at 20% and accrete to their face value over their terms by recording interest expense, and by securing a $32.0 million term loan from Silicon Valley Bank. We used the proceeds from the term loan to retire convertible partner debt from Elan and BI. The retired convertible partner debt was due from 2003 to 2005 and carried interest rates from 8.5% to 12%. The term loan bears interest at the prime rate, which was 4.0% at December 31, 2003. We can convert the interest to a fixed rate at our option at any time at the then-applicable prime rate plus 1.25%. The increase in our debt and other obligations in 2003 was offset by Lilly's waiver on repayment of the $21.2 million manufacturing loan it provided to us to build the Affinitak manufacturing facility, of which we had $15.4 million outstanding at December 31, 2002. In addition, we repaid principal and interest related to certain of our partner debt and certain of our capital leases. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing to maintain our working capital as long as the terms remain commercially attractive. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe that our available cash, cash equivalents and short-term investments as of December 31, 2003, when combined with investment income and committed contractual cash payments from our partners, will be sufficient to meet our anticipated requirements for at least the next 36 months. Due to the uncertainties in our business discussed in this section, and elsewhere in this report, including "Risk Factors" beginning on page 26, this may not be the case. In addition, we may choose to, or prevailing business conditions may require us to, obtain additional financing from time to time. We may choose to raise additional funds through public or private financing, licensing and contractual agreements or other arrangements. Additional funding, if needed, may not be available on terms favorable to us. Furthermore, any additional equity financing may be dilutive to our shareholders, and debt financing, if available, may involve restrictive covenants. If we choose to obtain funding through licensing and other contractual agreements, those agreements may require us to relinquish our rights to certain of our technologies or products. Our failure to raise capital when needed would harm our business, financial condition and results of operations.

The following table summarizes our contractual obligations as of December 31, 2003. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Standard Operating Debt	$ 38.4	$ 6.2	$ 18.6	$ 13.6	$ —
Convertible Partner Debt	$ 80.1	$ 6.4	$ 73.7	$ —	$ —
5 1/2% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ —	$ 125.0
Capital Leases and Other Obligations	$ 7.1	$ 3.9	$ 3.2	$ —	$ —
Operating Leases	$ 12.3	$ 2.7	$ 5.6	$ 2.7	$ 1.3

Our contractual obligations consist primarily of partner debt and publicly traded convertible debt that we can repay on favorable terms with equity. In addition, we also have standard operating debt, capital leases and other obligations. Convertible partner debt at December 31, 2003 included: 1) the interest-free loan Lilly made available to us to fund the joint research collaboration and 2) the remaining portion of the convertible debt provided by BI, associated with the collaborative agreement

between the two companies that we repaid in January 2004. Our standard operating debt includes a $32.0 million term loan from Silicon Valley Bank. Capital leases and other obligations consist of $6.3 million and $860,000 for capital leases and other obligations, respectively.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to BI and Elan. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate, which was 4.0% at December 31, 2003. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. We used the proceeds from the loan to pay off existing debt to Elan of $5.1 million plus accrued interest and to BI of $22.6 million plus accrued interest, of which $6.4 million plus accrued interest was paid off subsequent to December 31, 2003. The carrying value of the term loan at December 31, 2003 was $32.0 million.

In August 2001, Lilly made available to us a $100.0 million interest-free loan to fund the joint research collaboration between the two companies. The loan is interest-free and is repayable, at our option, in cash or common stock at $40 per share at the end of four years. The term of the loan provides for quarterly draw downs by us. As of December 31, 2003, we had drawn down $73.8 million of the $100.0 million available. We are accounting for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan was agreed to. We carry the net present value of the drawdowns as a long-term obligation and record interest expense over the term of the loan. The difference between the cash received and the present value of the loan represents value given to us by Lilly to help fund the research collaboration, and we account for the difference as deferred revenue related to the collaboration and recognize it as revenue over the period of performance. As of December 31, 2003, the balance in long-term obligations was $53.0 million and the balance in deferred revenue was $20.8 million.

During 1999 and 2000, in conjunction with the HepaSense and Orasense joint ventures, Elan made available to us credit facilities of up to $30.4 million, evidenced by convertible promissory notes. The terms of these notes provided for interest at 12% annually, with maturities through January 2006. The notes were convertible into our common stock at anytime by either party, at a rate determined by the underlying agreements. In July 2002, we prepaid $19.7 million of the then-outstanding debt with $14.7 million in cash, resulting in a gain of approximately $5.0 million for the year ended December 31, 2002. As of December 31, 2002, there was $7.2 million outstanding under the Orasense credit facility. We used the proceeds from our term loan from Silicon Valley Bank which we secured in December 2003, to repay these borrowings in full. We can no longer borrow funds against the Orasense and HepaSense credit facilities.

During 1997 and 1996, we borrowed a total of $22.6 million under a $40.0 million line of credit made available pursuant to the terms of our collaborative agreement with BI. Borrowings under the line of credit bore interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and ranged from 8.4% to 8.5%. Principal borrowings were repayable in cash or our common stock, at our option. We repaid $16.2 million, plus interest in the fourth quarter of 2003, and we repaid the remaining principal installment of $6.4 million, plus interest, in January 2004, using the proceeds from our Silicon Valley Bank term loan.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5 1/2%, which is payable semi-annually, and mature in May 2009. Upon maturity, holders of the subordinated notes can convert the notes into shares of common stock at a conversion price of $16.625 per share. At December 31, 2003 and 2002, the principal outstanding on the notes was $125.0 million.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2003 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to make expenditures to expand our research and development activities including our preclinical and clinical product development. We plan to continue to enter into more collaborations with partners to provide for additional revenue to us and we may be required to incur additional cash expenditures related to our obligations under many of the new agreements we may enter into. For example, we recently made a $10 million equity investment in Alnylam as part of our strategic alliance with them. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing

lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Prospective Information

DARPA Contract

In March 2004, we entered into a two-year contract with SAIC to further the development of our TIGER biosensor to identify infectious agents in biological warfare attacks. The contract provides for up to $19.5 million in funding by DARPA.

Strategic Alliance with Alnylam

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. As part of our agreement, we also made a $10.0 million equity investment in Alnylam. In turn, Alnylam nonexclusively licensed us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double stranded-RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to changes in interest rates primarily from our investments in certain securities classified as short-term investments and, secondarily, from our long-term debt arrangements. We invest our excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Item 8. Financial Statements and Supplementary Data.

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a)(1) and (2), and incorporated them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

There has been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2003 with our Independent Auditors.

Item 9A. Controls and Procedures.

As of the end of the period covered by this Annual Report on Form 10-K, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of the end of the year ended December 31, 2003.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART III

Item 10. Directors and Executive Officers of the Registrant.

We incorporate by reference the information required by this Item with respect to Directors and Audit Committee financial expert by reference from the information under the caption "Election of Directors" and "Audit Committee", respectively, contained in our definitive Proxy Statement (the "Proxy Statement"),

which we will file on or about April 15, 2004 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2003 Annual Meeting of stockholders to be held on May 26, 2004.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics" contained in the Proxy Statement. We have filed our Code of Ethics as an exhibit to this Report on Form 10-K.

Item 1, Part I of this Report contains the required information concerning our Executive Officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, from the information under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

Item 11. Executive Compensation.

We incorporate by reference the information required by this item to the information under the caption "Executive Compensation" and "Compensation Committee Interlock and Insider Participation" contained in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management.

We incorporate by reference the information required by this item to the information under the captions "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" contained in the Proxy Statement.

Item 13. Certain Relationships and Related Transactions.

We incorporate by reference the information required by this item to the information under the caption "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accounting Fees and Services.

We incorporate by reference the information required by this item to the information under the caption "Ratification of Selection of Independent Auditors" contained in the Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules, and Reports on Form 8-K.

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

See Index to Exhibits on pages 59 through 64.

(b) Reports on Form 8-K

On November 4, 2003, we filed a report on Form 8-K for the announcement of our third quarter results and the related press release dated November 4, 2003. We furnished this information under Item 12 of Form 8-K, "Results of Operations and Financial Condition."

On January 5, 2004, we filed a report on Form 8-K for the announcement of data from a Phase 2 clinical trial which demonstrate that ISIS 104838, and antisense TNF-alpha inhibitor, produced a statistically significant disease response in patients with rheumatoid arthritis.

On February 10, 2004, we filed a report on Form 8-K for the announcement of our financial results for the year ended December 31, 2003 and the related press release dated February 10, 2004. We furnished this information under Item 12 of Form 8-K, "Results of Operations and Financial Condition."

(c) Exhibits

We listed the exhibits required by this Item under Item 15(a)(3).

(d) Financial Statement Schedules

We have provided the information required by this Item under Item 15(a)(2).

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 12th day of March, 2004.

ISIS PHARMACEUTICALS, INC.
By: /s/ STANLEY T. CROOKE, M.D., PH.D.

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke and B. Lynne Parshall, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	March 12, 2004
/s/ B. LYNNE PARSHALL, J.D. B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 12, 2004
/s/ SPENCER R. BERTHELSEN, M.D. Spencer R. Berthelsen, M.D.	Director	March 12, 2004
/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 12, 2004
/s/ FREDERICK T. MUTO, J.D. Frederick T. Muto	Director	March 12, 2004
/s/ JOHN C. REED, M.D., PH.D John C. Reed, M.D., Ph.D.	Director	March 12, 2004

/s/ MARK B. SKALETSKY Mark B. Skaletsky	Director	March 12, 2004
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 12, 2004

INDEX TO EXHIBITS

Exhibit Number	Description of Document

3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001.(19)
3.3	Bylaws.(19)
4.1	Certificate of Designation of the Series A Convertible Preferred Stock.(11)
4.2	Certificate of Designation of the Series B Convertible Preferred Stock.(14)
4.3	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	Specimen Common Stock Certificate.(1)
4.5	Specimen Series A Preferred Stock Certificate.(18)
4.6	Specimen Series B Preferred Stock Certificate.(18)
4.7	Form of Right Certificate.(17)
4.8	Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(6)
4.9	First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(7)
4.11	Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Orasense Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(12)
4.13	Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(14)
4.14	Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.15	Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.16	Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.17	Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(16)
4.18	Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 5 1/2% Convertible Subordinated Notes due 2009.(16)

4.19	Form of 5 1/2% Convertible Subordinated Note due 2009.(16)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2*	Registrants 1989 Stock Option Plan, as amended.(6)
10.3*	Registrants 1992 Non-Employee Directors Stock Option Plan, as amended.(4)
10.4*	Registrants Employee Stock Purchase Plan.(10)
10.5	Form of Employee Assignment of Patent Rights.(1)
10.6*	Registrants 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.7	Agreement between the Registrant and CIBA Vision Corporation (now Novartis Ophthalmics AG) dated July 10, 1997 (with certain confidential information deleted).(5)
10.8	Amendment No. 2 to the Agreement between the Registrant and CIBA Vision Corporation dated September 14, 1998 (with certain confidential information deleted).(8)
10.9	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $6,000,000, together with the related Deed of Trust

	and Assignment of Rents dated March 24, 1997.(5)
10.10	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $3,706,620, together with the related Deed of Trust and Assignment of Rents dated March 24, 1997.(5)
10.11	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.12	Research Collaboration and License Agreement between Merck & Co., Inc. and the Registrant dated June 1, 1998 (with certain confidential information deleted).(7)
10.13	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.14	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.15	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.16	Development and License Agreement, dated August 14, 2001 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(20)
10.17	Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.18	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.19	Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.20	Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)

10.21	Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.22	Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc.(22)
10.23	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.24	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.25	Collaboration Agreement dated December 11, 2001 between the Registrant and Amgen Inc.(24)
10.26	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.27	Amendment No. 1 to Securities Purchase Agreement dated January 14, 2000, between the Registrant and Elan International Services, Ltd. (with certain confidential information deleted).(27)
10.28	Letter Agreement dated April 24, 2002 between the Registrant and Reliance Insurance Company.(26)
10.29	Amended and Restated Collaboration Agreement dated June 17, 2002, between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(27)
10.30	Settlement, Release, and License Grant Agreement dated September 6, 2002, between the Registrant and Sequitur, Inc. (with certain confidential information deleted).(28)
10.31	Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.32	Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.33	Amended and Restated Subscription, Joint Development and Operating Agreement among the Registrant, Elan Corporation, Plc., Elan International Services, Ltd. and Orasense Ltd., dated October 24, 2002 (with certain confidential information deleted).(30)
10.34	Termination Agreement among the Registrant, Elan Corporation, Plc., Elan Pharma International Limited, Elan International Services, Ltd. and HepaSense Ltd., dated November 5, 2002.(30)
10.35	Registrant's restated 10b5-1 Trading Plan.(29)
10.36	Registrant's 2002 Non-Employee Directors' Stock Option Plan.(31)

10.37	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(31)
10.38	Waiver and Release Agreement dated June 5, 2003 between the Registrant and Eli Lilly and Company (with certain confidential information deleted). (32)

10.39	Amendment Number One to Development and License Agreement dated June 5, 2003 between the Registrant and Eli Lilly and Company (with certain confidential information deleted). (32)
10.40	Initial Collaboration Agreement dated June 23, 2003 between the Registrant and Industrial Technology Research Institutes (with certain confidential information deleted). (32)
10.41	Form of Severance Agreement dated April 2003 entered into between the Registrant and its executive officers and certain key employees, together with related schedule. (32)
10.42	Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted). (33)
10.43	Amendment No. 1 to Isis Pharmaceuticals Inc. 2000 Employee Stock Purchase Plan. (33)
10.44	Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement.
10.45	Grant letter dated October 31, 2003 from the Singapore Economic Development Board to ISIS Pharmaceuticals Singapore Pte Ltd (with certain confidential information deleted)
10.46	Development agreement dated on November 12, 2004 between the Registrant and RoboDesign International, Inc. (with certain confidential information deleted)
14.1	Registrant's Code of Ethics and Business Conduct
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Ernst & Young LLP, Independent Auditors.
24.1	Power of Attorney. Reference is made to page 57.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. (from Q3 03)
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. (from Q3 03)
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
99.2	Form of Confidentiality Agreement.(11)

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

(2) Not used

(3) Not used

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1998 and incorporated herein by reference.

(9) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.

(10)

Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.

(11) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

(12) Filed as an exhibit to the Registrant's Report on Form 8-K dated April 20, 1999 and incorporated herein by reference.

(13) Not used

(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2000 and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.

(17) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

(18) Filed as an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.

(19) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.

(20) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

(21) Filed as an exhibit to the Registrant's Report on Form 8-K dated October 29, 2001 and incorporated herein by reference.

(22) Filed as an exhibit to the Registrant's Report on Form 8-K dated December 12, 2001 and incorporated herein by reference.

(23) Not used

(24) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 4, 2002 and incorporated herein by reference.

(25) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 7, 2002 and incorporated herein by reference.

(26) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended March 31, 2002 and incorporated herein by reference.

(27) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2002 and incorporated herein by reference.

(28) Filed as an exhibit to the Registrant's Report on Form 8-K dated September 16, 2002 and incorporated herein by reference.

(29) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2002 and incorporated herein by reference.

(30) Filed as an exhibit to the Registrant's Report on Form 8-K dated November 6, 2002 and incorporated herein by reference.

(31) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2001 and incorporated herein by reference.

(32) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2003 and incorporated herein by reference.

(33) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended September 30, 2003 and incorporated herein by reference.

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

ISIS PHARMACEUTICALS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors and Stockholders
Isis Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2003 and 2002, and the related consolidated statements of operations, consolidated stockholders' equity, and consolidated cash flows for each of the three years in the period ended December 31, 2003. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

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

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc. at December 31, 2003 and 2002, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2003, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

San Diego, California
January 26, 2004, except for Note 12, as to which the date is March 11, 2004.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(in thousands, except share data)

	December 31,	
	2003	2002
ASSETS		
Current assets:		
Cash and cash equivalents	$ 33,117	$ 101,856
Short-term investments	182,387	187,497
Contracts receivable	2,657	14,906
Inventory	13,995	11,090
Other current assets	7,405	4,831
Total current assets	239,561	320,180
Property, plant and equipment, net	34,790	59,094
Licenses, net	28,363	30,749
Patents, net	22,374	18,904
Deposits and other assets	8,479	9,186
Long-term investments	1,375	570
Total assets	$ 334,942	$ 438,683
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,720	$ 5,524
Accrued compensation	4,149	3,330
Accrued liabilities	6,527	6,794
Amount due to affiliates	—	5,193
Current portion of long-term obligations	16,477	21,435
Current portion of deferred contract revenue	14,684	33,674

Total current liabilities	45,557	75,950
5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	88,397	67,893
Long-term deferred contract revenue, less current portion	8,810	14,363
Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 issued and outstanding at December 31, 2003 and 2002	12,015	12,015
Accretion of Series B Preferred stock dividends	2,560	1,866
Common stock, $.001 par value; 100,000,000 shares authorized 55,557,253 and 55,215,785 shares issued and outstanding at December 31, 2003 and 2002, respectively	56	55
Additional paid-in capital	604,948	602,101
Deferred compensation	(294)	(59)
Accumulated other comprehensive income (loss)	3,476	(608)
Accumulated deficit	(555,583)	(459,893)
Total stockholders' equity	67,178	155,477
Total liabilities and stockholders' equity	$ 334,942	$ 438,683

See accompanying notes

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

	Years Ended December 31,		
	2003	2002	2001
Revenue			
Research and development revenue under collaborative agreements	$ 49,467	$ 67,820	$ 40,396
Research and development revenue from affiliates	—	11,942	10,561
Licensing and royalty revenue	523	417	2,316
Total revenue	49,990	80,179	53,273
Expenses			
Research and development not including compensation (benefit) related to stock options of $673, $(2,018), and $3,244 in 2003, 2002 and 2001, respectively	116,963	124,074	83,741
General and administrative not including compensation (benefit) related to stock options of $240, ($984), and $1,329 in 2003, 2002, and 2001, respectively	9,289	8,547	11,061
Compensation (benefit) related to stock options	913	(3,002)	4,573
Restructuring activities	1,803	1,373	—
Total operating expenses	128,968	130,992	99,375
Loss from operations	(78,978)	(50,813)	(46,102)
Equity in loss of affiliates	—	(16,011)	(18,840)
Investment income	5,100	8,462	6,358
Interest expense	(18,680)	(16,562)	(15,248)
Loss on investment	(2,438)	—	—
Loss on prepayment of 14% Notes	—	(2,294)	—
Gain on prepayment of 12% Notes	—	4,976	—
Net loss	(94,996)	(72,242)	(73,832)
Accretion of dividends on preferred stock	(694)	(1,060)	(1,299)
Net loss applicable to common stock	$ (95,690)	$ (73,302)	$ (75,131)
Basic and diluted net loss per share	$ (1.73)	$ (1.35)	$ (1.70)

Shares used in computing basic and diluted net loss per share	55,463	54,480	44,109

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2003, 2002 and 2001
(in thousands)

Description	Preferred stock Shares	Preferred stock Amount	Preferred stock Dividend Accretion	Common stock Shares	Common stock Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total Stockholders' Equity
Balance at December 31, 2000	132	$ 24,030	$ 1,634	40,086	$ 40	$ 352,854	$ (858)	$ 126	$ (311,460)	$ 66,366
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(75,131)	(75,131)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	534	—	534
Comprehensive loss	—	—	—	—	—	—	—	—	—	(74,597)
Dividends accrued on preferred stock	—	—	1,299	—	—	—	—	—	—	1,299
Deferred compensation	—	—	—	—	—	3,960	(3,960)	—	—	—
Issuances of common stock, net of offering costs	—	—	—	12,760	13	218,213	—	—	—	218,226
Options exercised and Employee stock purchase plan	—	—	—	904	1	7,231	—	—	—	7,232
Compensation relating to the granting of options	—	—	—	—	—	—	4,573	—	—	4,573
Balance at December 31, 2001	132	$ 24,030	$ 2,933	53,750	$ 54	$ 582,258	$ (245)	$ 660	$ (386,591)	$ 223,099
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(73,302)	(73,302)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(1,268)	—	(1,268)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(74,570)
Dividends accrued on preferred stock	—	—	1,060	—	—	—	—	—	—	1,060
Deferred compensation	—	—	—	—	—	(3,188)	3,188	—	—	—
Options exercised and employee stock purchase plan	—	—	—	683	1	5,139	—	—	—	5,140
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(3,002)	—	—	(3,002)
Issuance of common stock				126		3,750				3,750
Conversion of preferred stock into common stock	(120)	(12,015)	(2,127)	657	—	14,142	—	—	—	—
Balance at December 31, 2002	12	$ 12,015	$ 1,866	55,216	$ 55	$ 602,101	$ (59)	$ (608)	$ (459,893)	$ 155,477
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(95,690)	(95,690)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	4,084	—	4,084
Comprehensive loss	—	—	—	—	—	—	—	—	—	(91,606)
Dividends accrued on preferred stock	—	—	694	—	—	—	—	—	—	694
Deferred compensation	—	—	—	—	—	1,148	(1,148)	—	—	—
Options exercised and employee stock purchase plan	—	—	—	341	1	1,699	—	—	—	1,700
Compensation relating to the granting of options	—	—	—	—	—	—	913	—	—	913
Balance at December 31, 2003	12	$ 12,015	$ 2,560	55,557	$ 56	$ 604,948	$ (294)	$ 3,476	$ (555,583)	$ 67,178

See accompanying notes

CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Years Ended December 31,		
	2003	2002	2001
Operating activities:			
Net loss	$ (94,996)	$ (72,242)	$ (73,832)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	8,551	5,985	4,924
Amortization of Patents	1,217	927	665
Amortization of Licenses	2,485	2,512	1,378
Compensation (benefit) related to stock options	913	(3,002)	4,573
Deferred interest on long-term debt	5,369	8,634	12,017
Loss on prepayment of 14% notes	—	2,294	—
Gain on prepayment of 12% notes	—	(4,976)	—
Accrued interest on prepayment of debt	—	(34,706)	—
Equity in losses of affiliates	—	16,011	18,840
Loss of investments	2,438	—	515
Non-cash expenses related to patents and fixed assets	2,813	1,622	157
Gain on disposal of property, plant and equipment	—	(260)	(570)
Changes in operating assets and liabilities:			
Contract receivable	12,249	(4,546)	(7,014)
Inventory	(2,905)	(11,090)	—
Other current and long-term assets	962	7,106	(1,842)
Accounts payable	(1,804)	(2,147)	3,796
Accrued compensation	819	(2,316)	2,048
Accrued liabilities	(267)	2,812	2,943
Deferred contract revenues	(33,318)	(6,999)	25,244
Net cash used in operating activities	(95,474)	(94,381)	(6,158)
Investing activities:			
Purchase of short-term investments	(152,910)	(200,563)	(334,032)
Proceeds from the sale of short-term investments	156,943	196,075	236,236
Purchases of property, plant and equipment	(7,554)	(36,834)	(9,287)
Proceeds from the disposal of property, plant and equipment	—	—	500
Licenses and other assets	(6,404)	(9,536)	(28,674)
Investments in affiliates	(5,193)	(9,511)	(8,229)
Net cash used in investing activities	(15,118)	(60,369)	(143,486)
Financing activities:			
Net proceeds from issuance of equity	1,700	8,890	210,458
Proceeds from 5.5% convertible subordinated notes	—	125,000	—
Proceeds from long-term borrowing	67,049	52,334	31,363
Principal payments on prepayment of debt	—	(52,704)	—
Principal payments on debt and capital lease obligations	(26,896)	(3,925)	(4,781)
Net cash provided by financing activities	41,853	129,595	237,040
Net increase (decrease) in cash and cash equivalents	(68,739)	(25,155)	87,396
Cash and cash equivalents at beginning of year	101,856	127,011	39,615
Cash and cash equivalents at end of year	$ 33,117	$ 101,856	$ 127,011
Supplemental disclosures of cash flow information			
Interest paid	$ 12,778	$ 39,333	$ 3,514
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt for patent acquisitions	$ —	$ —	$ 13,500
Additions to debt for licensing costs	$ —	$ 1,050	$ —
Additions to deposits and other assets from sale of equipment	$ —	$ 300	$ —
Additions to other current assets from sale of equipment	$ —	$ 160	$ —
Additions to long-term investment for acquired corporate securities	$ 750	$ —	$ —
Repayment of debt with common stock	$ —	$ —	$ 15,000
Conversion of preferred stock into common stock	$ —	$ 14,142	$ —
Addition to obligations for acquisition of property, plant and equipment	$ —	$ —	$ 1,184
Additions to long-term investment and deferred revenue for acquired corporate securities	$ —	$ —	$ 2,759
Decrease in inventory and deferred revenue	$ 8,750	$ —	$ —
Decrease in property plant and equipment and notes payable	$ 21,200	$ —	$ —

ISIS PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2003

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis and its wholly-owned subsidiary, Isis Pharmaceuticals Singapore Pte Ltd. There were no current operations or results of operations for the wholly-owned subsidiary for the year ended December 31, 2003.

Organization and business activity

Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, Isis Pharmaceuticals was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc. ("Isis" or the "Company"), in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share

Isis follows provisions of Statement of Financial Accounting Standards (SFAS) No. 128 *Earnings per Share*. Isis computes basic loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period ("Basic EPS method"). Isis computes diluted earnings (loss) per common share using the weighted-average number of common and dilutive common equivalent shares outstanding during the period ("Diluted EPS method"). Diluted common equivalent shares of 17.1 million at December 31, 2003 consisted of shares issuable upon exercise of stock options, warrants, convertible debt and conversion of preferred stock. As Isis incurred a loss in the years ended December 31, 2003, 2002 and 2001, Isis did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be antidilutive.

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and Isis records contract revenue as earned based on the performance requirements of Isis' collaborative research and development contracts. Isis recognizes contract fees for which no further performance obligations exist when Isis receives the payments or when Isis is reasonably certain it can collect the receivable. Isis records payments received in excess of amounts earned as deferred contract revenue. The company expenses research and development costs as incurred. For the years ended December 31, 2003, 2002 and 2001, research and development costs of approximately $30.2 million, $68.3 million and $59.2 million, respectively, were related to collaborative research and development arrangements.

Revenue recognition

Isis recognizes revenue when Isis satisfies all contractual obligations and Isis is reasonably certain it can collect the receivable.

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the

contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with *Emerging Issues Task Force Issue No. 00-21* ("EITF 00-21") *Accounting for Revenue Arrangements with Multiple Deliverables*. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis records revenue from federal research grants during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products. Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured. This statement has not had a material impact on the Company's operating results and financial position.

As part of Isis' alliance with Eli Lilly and Company ("Lilly") in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of December 31, 2003, Isis had drawn down $73.8 million on the $100.0 million loan. Isis discounted the $73.8 million loan to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accretes the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represents value Lilly gave to Isis to help fund the research collaboration. Isis accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Research and development revenue from affiliates

In late 2002, Isis terminated its HepaSense and Orasense collaborations with Elan Corporation plc ("Elan") and as a result, Isis no longer earns revenue from these collaborations.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which Isis is not required to provide services in the future.

Concentration of credit risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. Isis and its audit committee established guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, cash equivalents and short-term investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income and these amounts have not been material. During the first quarter of 2003, Isis recorded a non-cash loss of $2.4 million related to the impairment of its equity investments in Antisense Therapeutics Limited ("ATL") and Hybridon, Inc. ("Hybridon"). This charge reflected the then-current market climate and was associated with the decline in market value of the equity investments from their initial valuations and Isis determined the decline in value to be other-than-temporary. In the second, third and fourth quarters of 2003, Isis recorded net unrealized gains related to its equity investments in ATL and Hybridon as a separate component of stockholders' equity. This reflected the increase in the market value of the investments since the first quarter of 2003.

Inventory Valuation

Isis' inventory includes drugs with alternative uses that are used primarily for its clinical development activities and drug products it manufactures for its partners under contractual terms. Isis states its inventory at the lower of cost or market, with cost determined under the first-in, first-out method. Isis reviews inventory periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. In the second quarter of 2003, Isis reduced the carrying value of its raw materials related to Affinitak to zero.

Inventory includes the following categories as of December 31, 2003 and 2002 (net realizable value in thousands):

	December 31,	
	2003	2002
Raw materials	$ 1,526	$ 10,186
Work in process	9,920	904
Finished goods	2,549	—
	$ 13,995	$ 11,090

The composition of inventory among raw materials, work-in-process and finished goods fluctuates from period-to-period based on the nature and timing of Isis' manufacturing activities in response to product requirements to support clinical trials and partner collaborations.

Property, plant and equipment

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

	December 31,	
	2003	2002
Land	$ 1,163	$ 1,163
Buildings and improvements	29,859	37,870
Equipment and computer software	49,108	58,274
Furniture and fixtures	3,356	2,224
	83,486	99,531
Less accumulated depreciation	(48,696)	(40,437)

	$ 34,790	$ 59,094

During 2003, Isis reduced to zero approximately $21.2 million in buildings, building improvements and equipment related to the debt repayment waiver Lilly granted Isis for amounts Lilly loaned Isis to fund the construction of a new manufacturing suite dedicated to the commercial production of Affinitak.

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

Building	31.5 years
Building improvements	15 years
Manufacturing facilities	10 years
Equipment	5 years
Computer software	3 years
Furniture and fixtures	5 years

Leasehold improvements are depreciated using the shorter of the remaining lease term or 10.7 years.

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. Isis' license from Hybridon comprises the majority of the license balance as of December 31, 2003 and 2002. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between six years and 15 years. Accumulated amortization related to licenses was $7.5 million and $5.0 million at December 31, 2003 and 2002, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.5 million for each of the years ending December 31, 2004, 2005, 2006, 2007 and 2008.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews costs regularly to determine that they include costs for patent applications Isis is pursuing. Isis evaluates costs related to patents that the company is not actively pursuing for impairment and writes off any patents, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued. The weighted average remaining

life of issued patents was 6.5 years and 7.0 years at December 31, 2003 and 2002, respectively. Accumulated amortization related to patents was $4.4 million and $3.2 million at December 31, 2003 and 2002, respectively. Based on existing patents, estimated amortization expense related to patents is as follows (in thousands):

Years Ending December 31,	Amortization (in thousands)
2004	$ 1,207
2005	$ 1,191
2006	$ 1,137
2007	$ 1,024
2008	$ 937

Investment in affiliates

Isis uses the equity method of accounting to account for its investments in 50% or less owned companies over which it has the ability to exercise significant influence. Isis also accounted for investments in its joint ventures, Orasense and HepaSense, using the equity method of accounting. At December 31, 2003 and 2002, Isis had the following investments accounted for using the equity method:

Orasense and HepaSense

In April 1999, Isis and Elan formed Orasense, Ltd., a Bermuda limited company. In January 2000, Isis and Elan formed HepaSense, Ltd., a Bermuda limited company. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. While Isis owned 80.1% of the outstanding common stock of Orasense and HepaSense, throughout the respective terms of the collaborations related to the joint ventures, Elan and its subsidiaries retained significant minority investor rights that were considered "participating rights" as defined in EITF 96-16. Accordingly, Isis accounted for its investment in each joint venture under the equity method of accounting for the years ended December 31, 2002 and 2001. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. See Note 6—Research and Development Collaborative Arrangements and Licensing Agreements for more detail on Isis' investment in Orasense and HepaSense.

Fair Value of Financial Instruments

Isis has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. Isis reports its investment securities at their estimated fair value based on quoted market prices of comparable instruments.

Long-lived assets

Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may have been impaired. Isis adopted SFAS 144, *Accounting for the Impairment of Long-Lived Assets*, and this standard has not had a material impact on the results of operations. For the year ended December 31, 2002, Isis recorded an impairment charge of $605,000 for the write-down of intellectual property related to the restructuring of the GeneTrove program.

Use of Esimates

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

Stock Based Compensation

In January 2000, Isis offered non-officer employees an opportunity to exchange certain of their existing out-of-the-money stock options for new options with exercise prices at the then-current market value. These options are required to be accounted for as variable stock options in accordance with Financial Interpretation No. 44 ("FIN 44"), *Accounting for Certain Transactions Involving Stock Compensation—an Interpretation of APB Opinion No. 25*. Isis reported the resulting compensation expense in the statement of operations. Variable stock options can result in significant increases and decreases in compensation expense, subject to the variability of Isis' stock price. As of December 31, 2002, optionholders had exchanged all of these options, or the options had expired.

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program") to maintain one of Isis' key assets, its employee base, in a manner that was sensitive to shareholder interests. The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options, granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options vest over three years beginning on January 1, 2003 and expire on December 31, 2008. Isis accounts for the affected options, until all these options have been exercised or cancelled, using variable accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded compensation expense of approximately $886,000 in 2003 and will continue to account for the affected options using variable accounting.

Isis has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense, except primarily for compensation expense related to the affected options from the 2000 and 2003 option exchange programs, for the Isis stock option plans and the employee stock purchase plan ("ESPP"). Had Isis determined compensation expense consistent with SFAS 123, Isis would have reported the following proforma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	2003	2002	2001
Net loss applicable to common stock—as reported	$ (95,690)	$ (73,302)	$ (75,131)
Net loss applicable to common stock—pro forma	$ (101,099)	$ (95,329)	$ (83,830)
Basic and diluted net loss per share—as reported	$ (1.73)	$ (1.35)	$ (1.70)
Basic and diluted net loss per share—pro forma	$ (1.82)	$ (1.75)	$ (1.90)

For purposes of proforma disclosures, Isis estimated, the fair value of each option grant and ESPP purchase rights on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Stock Options			ESPP		
	2003	2002	2001	2003	2002	2001
Risk—free interest rate	4.3%	3.8%	4.5%	4.3%	3.8%	4.5%
Dividend yield	0%	0%	0%	0%	0%	0%
Volatility	69.5%	78.7%	79.1%	49.5%	80.9%	85.9%
Expected Life	6.2 years	5.4 years	5.7 years	6 months	6 months	6 months

The weighted average fair value of options granted was $5.70 for 2003, $11.34 for 2002, and $12.14 for 2001. The weighted average fair value of the ESPP purchase rights was $4.46, $5.60, and $8.45 for 2003, 2002 and 2001, respectively.

Comprehensive income (loss)

SFAS 130, *Reporting Comprehensive Income* ("SFAS 130") requires Isis to display comprehensive income (loss) and its components as part of Isis' full set of consolidated financial statements. The measurement and presentation of net income (loss) did not change. Comprehensive income (loss) is comprised of net income (loss) and certain changes in equity that are excluded from net income (loss). Specifically, SFAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which Isis reported separately in stockholders' equity, to be included in accumulated other comprehensive income (loss). Comprehensive income (loss) for the years ended December 31, 2003, 2002 and 2001 has been reflected in the Consolidated Statements of Stockholders' Equity.

Impact of recently issued accounting standards

In December 2003, the Securities Exchange Commission ("SEC") issued Staff Accounting Bulletin No. 104 ("SAB 104"), *Revenue Recognition*, which updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 ("SAB 101") *Revenue Recognition in Financial Statements*, in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured. The adoption of SAB 104 has not had a material impact on Isis' operating results and financial position.

In May 2003, the FASB issued SFAS No. 150, *"Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity."* The statement is effective for financial instruments entered into or modified after May 31, 2003, and otherwise is effective at the beginning of the first interim period beginning after June 15, 2003. This statement establishes standards for how an issuer classifies and measures certain financial instruments with characteristics of

both liabilities and equity. It requires that an issuer reclassify certain instruments previously classified as equity as a liability. The adoption of this Statement did not have an impact on Isis' consolidated financial statements.

In January 2003, the FASB issued FASB Interpretation No. 46 ("FIN 46"), *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of variable interest entities ("VIE"s) either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. In December 2003, the FASB completed deliberations of proposed modifications to FIN 46 ("Revised Interpretations") resulting in multiple effective dates based on the nature as well as the creation date of the VIE. VIEs created after January 31, 2003, but prior to January 1, 2004, may be accounted for either based on the original interpretation or the Revised Interpretations. However, the Revised Interpretations must be applied no later than Isis' quarter ended March 31, 2004. VIEs created after January 1, 2004 must be accounted for under the Revised Interpretations. Special Purpose Entities ("SPE"s) created prior to February 1, 2003 may be accounted for under the original or Revised Interpretation's provisions no later than the quarter ended December 31, 2003. Non-SPEs created prior to February 1, 2003, should be accounted for under the Revised Interpretation's provisions no later than Isis' quarter ended March 31, 2004. As of December 31, 2003, Isis had a collaborative arrangement with a development stage biopharmaceutical company developing drugs based on RNA splicing technology. Isis considers this entity to be a VIE under the provisions of FIN 46. During 2003 and early 2004, Isis advanced $500,000 and $250,000, respectively, in cash in exchange for a promissory note convertible into equity, pursuant to a qualified financing, as defined by the underlying agreement. To date, Isis has contributed the substantial portion of this entity's funding. Due to the uncertainty in ultimately realizing any value from the consideration paid, Isis expensed the payments when made. As a result, Isis expects that the adoption of FIN 46 will not have a material impact on its operating results and financial position.

2. Investments

Isis invests its excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to maximize trends in yields and interest rates without compromising safety and liquidity. The following table summarizes the contract maturity of debt securities held by Isis as of December 31, 2003:

Less than 1 year	37%
1 - 3 years	60%
3 - 5 years	3%
Total	100%

Isis has an ownership interest of less than 20% each in two public and two private companies it conducts business with, and accounts for them under the cost method of accounting according to APB 18. The companies include ATL and Hybridon, which are publicly-traded, and Santaris Pharma A/S ("Santaris") and OncoGenex Technologies, Inc. ("OncoGonex"), which are privately-held. In determining if and when a decrease in market value below Isis' cost is other-than-temporary in its equity positions, Isis examines historical trends in stock price, the financial condition and near term prospects of the issuer, and Isis' current need for cash. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the period operating results to the extent of

the decline. See Note 1—Organization and Significant Accounting Policies for discussion of impairment loss incurred in 2003.

The following is a summary of Isis' investments accounted for as available-for-sale securities (in thousands):

	Available-for-Sale Securities		
	Cost	Unrealized Gains (Losses)	Estimated Fair Value
December 31, 2003			
U.S. Treasury securities and obligations of U.S. government agencies	$ 90,728	$ 142	$ 90,870
U.S. corporate debt securities	90,905	612	91,517
Corporate equity securities	3,424	2,722	6,146
Total	$ 185,057	$ 3,476	$ 188,533
Less current portion included in short-term investments	181,633	754	182,387
Less current portion included in other current assets	2,049	2,722	4,771
Non-current portion included in long-term investments	$ 1,375	$ —	$ 1,375

	Available-for-Sale Securities		
	Cost	Unrealized Gains (Losses)	Estimated Fair Value
December 31, 2002			

U.S. Treasury securities and obligations of U.S. government agencies	$ 89,607	$ 758	$ 90,365
U.S. corporate debt securities	96,202	930	97,132
Corporate equity securities	5,045	(2,296)	2,749
Total	$ 190,854	$ (608)	$ 190,246
Less current portion included in short-term investments	185,809	1,688	187,497
Less current portion included in other current assets	4,475	(2,296)	2,179
Non-current portion included in long-term investments	$ 570	$ —	$ 570

3. Long-Term Obligations and Commitments

Long-term obligations consisted of the following (in thousands):

	December 31,	
	2003	2002
Standard Operating Debt	$ 38,392	$ 5,702
5 1/2% Convertible Subordinated Notes	125,000	125,000
Convertible Partner Debt		
Eli Lilly	73,750	62,843
Elan	—	7,219
Boehringer Ingleheim	6,376	22,576
Abbott	—	1,019
Total Convertible Partner Debt	80,126	93,657
Capital Leases and Other Obligations	7,116	9,469
Total	250,634	233,828
Less: Current Portion	(16,477)	(21,435)
Less: Eli Lilly Debt Classified as Deferred Revenue	(20,760)	(19,500)
Total Long-Term Obligations	$ 213,397	$ 192,893

Standard Operating Debt

In December 2003, Isis obtained a $32.0 million term loan from Silicon Valley Bank. The term loan is secured by substantially all of Isis' operating assets, excluding intellectual property, real estate, and certain equity investments. The term loan bears interest at the prime rate (4% at December 31, 2003), is payable in equal monthly payments of principal and interest, matures in December 2008, and is convertible at the election of Isis to a fixed rate at the then-applicable prime rate plus 1.25%. The term loan is subject to certain liquidity and other covenants, including a requirement that Isis maintain a minimum balance in an account at the lending bank at all times equal to the outstanding balance of the loan. Isis used the proceeds of the loan to pay off the Elan and Boehringer Ingelheim ("BI") partner debt in late 2003 and early 2004. The carrying value of this loan at December 31, 2003 was $32.0 million, which approximated fair value.

In December 2002, Isis obtained a credit facility evidenced by promissory notes of up to $6.7 million from a bank to refinance two existing notes. The loan is secured by Isis' real property and bears interest at the prime rate plus 0.5% (4.5% at December 31, 2003), is payable in monthly payments of principal and interest, with the final principal payment due on December 2006. Isis borrowed its final installment of $998,000 on this loan in January 2003. The carrying value of this loan at December 31, 2003 and 2002 was $6.4 million and $5.7 million respectively, which approximated fair value.

Convertible Subordinated Debt

In May 2002, Isis completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. Isis includes the issuance costs in the balance sheet under Deposits and Other Assets and is amortizing these issuance costs to interest expense over the life of the debt. The subordinated notes bear interest at 5 1/2%, which is payable

semi-annually, and mature in May 2009. The notes are convertible into shares of common stock at a conversion price of $16.625 per share. At December 31, 2003 and 2002, the principal and accrued interest outstanding on the notes was $125.0 million and $1.1 million, respectively. The fair value of the subordinated notes was $101.2 million and $90.1 million as of December 31, 2003 and 2002, respectively.

Isis used a portion of the net proceeds from the convertible notes to prepay amounts outstanding on its 14% Senior Subordinated Notes, and certain obligations under its credit facilities with Elan. These early debt retirements resulted in a $2.3 million loss on prepayment of 14% Notes and a $5.0 million gain on prepayment of 12% Notes, and are included as such on the accompanying Consolidated Statements of Operations for the year ended December 31, 2002.

Convertible Partner Debt

Eli Lilly

In September 2002, pursuant to a manufacturing agreement, Lilly provided to Isis a $21.2 million loan to fund the construction of a new manufacturing suite dedicated to the commercial production of Affinitak. The movable equipment purchased for the manufacturing suite secured the loan, which bore interest at prevailing market rates. In June 2003, as part of a renegotiation of the manufacturing relationship, Lilly waived repayment of the loan. As a result of the repayment waiver, Isis reduced to zero the values of the $21.2 million loan and property and equipment totaling $21.2 million related to the new manufacturing suite. As of December 31, 2002, $15.4 million was outstanding on this loan, which approximated fair value. There was no outstanding balance on this loan as of December 31, 2003.

In August 2001, Lilly made available to Isis a $100.0 million loan facility to fund joint research between the two companies. The loan is interest-free and payable, at Isis' option, in cash or common stock at $40 per share in August 2005. The loan facility provides for quarterly draw-downs by Isis in varying amounts. As of December 31, 2003 and 2002, Isis had drawn down $73.8 million and $47.5 million, respectively. Isis accounts for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan agreement was entered into. Isis carries the net present value of the draw-downs as a long-term obligation and records interest expense over the term of the loan. The difference between the cash received and the present value of the loan represents value Lilly gave Isis to help fund the research collaboration. Isis accounts for this difference as deferred revenue and recognizes it as research and development revenue under collaborative agreements over the period of performance. At December 31, 2003 and 2002, the balance in long-term obligations related to this loan was $53.0 million and $28.0 million, respectively, and the balance in deferred revenue was $20.8 million and $19.5 million, respectively.

Elan

During 1999 and 2000, in conjunction with the HepaSense and Orasense joint ventures, Elan made available to Isis credit facilities of up to $30.4 million, evidenced by convertible promissory notes. The terms of these notes provided for interest at 12% annually, with maturities through January 2006. The notes were convertible into the common stock of Isis at anytime by either party, as defined by the underlying agreements. In July 2002, Isis prepaid $19.7 million of the then-outstanding debt with $14.7 million in cash, resulting in a gain of approximately $5.0 million for the year ended December 31, 2002. As of December 31, 2002, there was $7.2 million outstanding under the Orasense credit facility.

Isis paid these borrowings in full from the proceeds of the company's term loan with Silicon Valley Bank in December 2003. Isis can no longer borrow funds against these credit facilities.

Boehringer Ingelheim

During 1997 and 1996, Isis borrowed a total of $22.6 million under a $40.0 million line of credit made available pursuant to the terms of its collaborative agreement with BI. Borrowings under the line of credit bore interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and ranged from 8.36% to 8.46%. Principal borrowings were repayable in cash or Isis common stock, at the option of Isis. In October 2003, Isis repaid the first installment of $8.3 million, plus interest. Isis repaid the remaining principal installments of $7.9 million, plus interest, and $6.4 million, plus interest, in December 2003 and January 2004, respectively, using the proceeds of the company's term loan with Silicon Valley Bank.

Abbott

In September 1999, Isis borrowed $1.0 million from Abbott for use as contribution toward costs associated with Abbott's design and construction of a facility for commercial scale manufacturing of oligonucleotides. The debt had an interest rate equal to 2% over the Citibank prime rate (6.75% at December 31, 2002), with interest payable annually. Borrowings under this facility at December 31, 2002 were $1.0 million which approximated fair value. In January 2003, Isis repaid all borrowings under this facility.

Capital Leases and Other Obligations

At December 31, 2003 and 2002, Isis had approximately $6.3 million and $8.3 million outstanding, respectively, under various capital equipment leases which bear interest at rates ranging from 6.22% to 10.34% and mature at various dates through 2006. At December 31, 2003 and 2002, Isis had approximately $860,000 and $1.2 million, respectively, under various contractual obligations, of which $700,000 and $1.1 million, respectively, represented amounts due to Integrated DNA Technologies, Inc. ("IDT") as part of the supply agreement entered into in December 2001. See Note 6—Research and Development Collaborative Arrangements and Licensing Agreements for more detail on Isis' agreement with IDT.

Annual debt and other obligation maturities at December 31, 2003 are as follows (in thousands):

2004	$ 13,010
2005	80,609
2006	12,145
2007	6,690
2008	6,924
Thereafter	125,000
Total	$ 244,378

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through July 2010. Two of the building leases have two extension options for five

years each. Annual future minimum payments under capital and operating leases as of December 31, 2003 are as follows (in thousands):

	Operating Leases	Capital Leases
2004	$ 2,738	$ 3,867
2005	2,765	2,474
2006	2,802	454
2007	1,705	—
2008	993	—
Thereafter	1,311	—
Total minimum payments	$ 12,314	$ 6,795
Less amount representing interest		(539)
Present value of future minimum payments		$ 6,256
Less current portion		(3,467)
Long-term portion		$ 2,789

Rent expense for the years ended December 31, 2003, 2002, and 2001 was $3.2 million, $2.9 million, and $2.3 million, respectively. Cost of equipment under capital leases at December 31, 2003 and 2002 was $20.7 million and $18.7 million, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2003 and 2002 was approximately $13.6 million and $10.3 million, respectively.

4. Stockholders' Equity

Preferred Stock

Isis is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2003, outstanding preferred stock consisted of Series B Convertible Exchangeable 5% Preferred Stock. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series A Convertible Exchangeable 5% Preferred Stock

In August 2002, the holder of the Company's Series A Convertible Exchangeable Preferred Stock exercised its option to convert the Series A shares into Isis common stock. The transaction converted the outstanding 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of Isis common stock using a conversion price of $21.54 per share. Included in the conversion was approximately $2.1 million in preferred stock dividends accrued in prior periods.

Series B Convertible Exchangeable 5% Preferred Stock

At December 31, 2003 and 2002, Isis had 16,620 shares authorized, of which 12,015 shares were issued and outstanding, of Series B Convertible Exchangeable 5% Preferred Stock. The shares have a term of six years and are convertible into Isis' common stock at $14.00 per share, which was 125% of the average closing price of Isis common stock for the 60 trading days ending two business days prior to June 30, 2002. In the event of a significant transaction, the shares are convertible into Isis' common stock at 125% of the average closing price of Isis' common stock for the 60 trading days ending two

business days prior to the significant transaction. The Preferred Stock is also exchangeable for the ownership Isis holds in HepaSense and bears a mandatory pay-in-kind dividend of 5.0% per year based on the original issue price per share, compounded semi-annually, payable only upon conversion into Isis' common stock or cash.

Series C Junior Participating Preferred Stock

In December 2000, Isis adopted a Preferred Share Purchase Rights Plan (the "Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right (a "Right") for each outstanding share of Isis common stock, par value $0.001 per share (the "Common Shares"), held of record at the close of business on January 10, 2001, and on each subsequently issued share of Isis common stock. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20% or more of Isis' common stock, the Rights permit the holders (other than the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share (the "Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share (the "Purchase Price"), subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and the qualifications, limitations and restrictions which make its value approximately equal to the value of a Common Share. Under certain conditions, Isis' Board of Directors may redeem the Rights in whole, but not in part, at a price of $0.001 per Right.

Common Stock

At December 31, 2003 and 2002, Isis had 100,000,000 shares authorized, of which 55,557,253 and 55,215,785 were issued and outstanding, respectively.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis' Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 10,200,000 shares of common stock to its employees, directors, and consultants. The plan also includes provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. Typically, options expire 10 years from the date of grant. Options granted after December 31, 1995 vest over a four year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. At December 31, 2003, a total of 2,689,000 options were outstanding, options to purchase 2,515,000 shares were exercisable, and 2,791,000 shares were available for future grant.

2000 Broad Based Equity Incentive Plan

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period,

with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan, pursuant to the April 2003 stock option exchange program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the optionee's employment or service as a consultant, employee or director. At December 31, 2003, a total of 5,198,000 options were outstanding, 1,928,000 shares were exercisable, and 539,000 shares were available for future grant.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 803,000 shares of common stock reserved for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2003, a total of 324,000 options were outstanding, 169,000 of the shares issued under this plan were exercisable and 460,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 2001 through December 31, 2003 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
Outstanding at December 31, 2000	7,671	$3.57 to $18.63	$ 9.21
Granted	1,893	$8.38 to $26.65	
Exercised	(817)	$3.57 to $18.00	
Terminated	(527)	$6.19 to $21.50	
Outstanding at December 31, 2001	8,220	$3.75 to $26.65	$ 9.88
Granted	2,197	$6.87 to $22.19	
Exercised	(505)	$4.00 to $17.88	
Terminated	(656)	$5.38 to $24.17	
Outstanding at December 31, 2002	9,256	$3.75 to $26.65	$ 11.34
Granted	2,724	$3.12 to $ 7.85	
Exercised	(35)	$4.00 to $6.81	
Terminated	(3,734)	$3.75 to $26.65	
Outstanding at December 31, 2003	8,211	$3.12 to $26.65	$ 8.66

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

	Options Outstanding			Options Exercisable	
Range of Exercise Price	Number Outstanding As of 12/31/03	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/03	Weighted Average Exercise Price
$3.12 - $4.98	519	4.73	$ 4.11	285	$ 3.99
$5.01 - $5.99	1,384	5.74	$ 5.23	73	$ 5.51
$6.02 - $6.95	2,754	7.00	$ 6.77	1,703	$ 6.78
$7.03 - $8.90	476	7.90	$ 8.08	219	$ 8.08
$9.01 - $9.95	829	7.08	$ 9.58	590	$ 9.59
$10.00 - $10.97	375	6.32	$ 10.32	315	$ 10.30
$11.00 - $12.94	1,009	5.56	$ 12.23	868	$ 12.33
$13.00 - $14.98	206	3.95	$ 13.69	197	$ 13.66
$15.00 - $17.95	312	7.72	$ 16.45	158	$ 16.29
$18.01 - $20.21	98	5.57	$ 18.61	74	$ 18.48
$21.05 - $26.65	249	7.99	$ 21.25	130	$ 21.25
	8,211			4,612	

Employee Stock Purchase Plan

In 2000, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan and Isis reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the 2000 Employee Stock Purchase Plan, resulting in a total of 800,000 shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. During 2003, 307,070 shares were issued under this plan to employees at prices ranging from $4.40 to $5.60 per share. At December 31, 2003, 200,138 shares were available for purchase under this plan.

Warrants

In 2002, Isis issued warrants to purchase 6,304 shares of common stock to Elan for the achievement of a development milestone related to the HepaSense joint venture between Isis and Elan. As of December 31, 2003, all of the warrants remained outstanding at an exercise price of $59.48 per share. The warrants expire April 25, 2007.

In 2000, Isis issued warrants to purchase 14,881 shares of common stock to Elan as part of the joint venture collaboration between Isis and Elan to form HepaSense. As of December 31, 2003, all of the warrants remained outstanding at an exercise price of $50.40 per share. The warrants expire May 1, 2008.

In 1999, Isis issued warrants to purchase 215,000 shares of common stock to Elan as part of the joint venture collaboration between Isis and Elan to form Orasense. As of December 31, 2003, all of

the warrants remained outstanding at an exercise price of $24 per share. The warrants expire April 19, 2004.

In 1997 and 1998, Isis issued warrants to purchase 500,000 and 300,000 shares of common stock, respectively, in conjunction with a private debt financing agreement. As of December 31, 2003, all of the warrants remained outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3 for further details.

As of December 31, 2003, total common shares reserved for future issuance was approximately 13,238,000.

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2003 and 2002 are shown below (in thousands). Isis had recognized valuation allowances of $235.0 million and $197.4 million for 2003 and 2002, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2003	2002
Deferred tax assets:		
Capitalized research expense	$ 86,827	$ 17,780
Net operating loss carry forwards	110,652	135,688
Research and development credits	30,095	24,634
Deferred revenue	9,573	19,573
Other, net	5,180	617
Total deferred tax assets	242,327	198,292
Deferred tax liabilities:		
Intangible Assets	(7,361)	(921)
Total deferred tax liabilities	(7,361)	(921)
Total net deferred tax assets	234,966	197,371
Valuation allowance for deferred tax assets	(234,966)	(197,371)
Net deferred tax assets	$ —	$ —

At December 31, 2003, approximately $6.5 million of the valuation allowance for deferred tax assets related to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2003, Isis had federal and California tax net operating loss carryforwards of approximately $312.1 million and $24.9 million, respectively. Isis also had federal and California research credit carryforwards of approximately $21.9 million and $11.9 million, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of California loss carryforwards. The federal tax loss carryforwards and the research credit carryforwards will begin expiring in 2007 and 2004, respectively, unless previously utilized. The California tax loss carryforwards will begin expiring in 2004, unless utilized.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of Isis' net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%. Isis believes that changes in ownership have occurred, but believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. Research and Development Collaborative Arrangements and Licensing Agreements

Drug Discovery, Development and Commercialization Collaborations

Singapore Economic Development Board

In November 2003, Isis received a grant of up to $8.0 million over three years from the Singapore Economic Development Board ("Singapore EDB"), which will fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with Severe Acute Respiratory Syndrome, or SARS. In connection with this grant, Isis established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary of Isis Pharmaceuticals, Inc. Isis recorded no revenue during 2003 related to this grant, and expects to begin earning revenue from this grant in the last half of fiscal 2004.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes of Taiwan, ("ITRI") to identify antisense candidates targeting the coronavirus associated with SARS. The collaboration entitled Isis to an upfront payment, milestone payments, and the potential for future funding. The milestones related to the identification of second-generation antisense drugs that inhibit SARS virus replication and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs as specified under the agreement. During 2003, Isis recorded revenue under this collaboration of $2.0 million, comprised of $1.0 million for an up-front payment and $1.0 million related to the achievement of certain milestones, as described above.

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1988 and September 2000, Isis entered into license agreements with Santaris, a privately-held company, formerly Pantheco, a privately-held company. The agreement was amended in May 2003. Under the terms of the amended and restated license agreements, Isis licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license is restricted to a limited number of molecular targets that are subject to Isis' approval. Santaris has agreed to pay Isis royalties on any products developed under the license.

As part of its original license agreements with Pantheco, Isis received shares of Pantheco common stock. In May 2003, Pantheco A/S and Cureon A/S merged to form Santaris Pharma A/S. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of antidilution provisions related to Pantheco's stock. After the merger and as of December 31, 2003, Isis' ownership interest in Santaris was less than 10%. Isis used the equity method of accounting for its investment in Pantheco in 2001, when Isis' ownership was in excess of 20%, and, accordingly, recorded $267,000 under equity in loss of affiliates during 2001. Isis did not record equity in loss of affiliates for 2003 and 2002 related to this investment, as Isis' ownership was less than 20%. After the merger and as of December 31, 2003, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheet at December 31, 2003 and

2002 includes a long-term investment at the lower of carrying value or fair market value of $625,000 and $570,000, respectively, related to this equity investment.

Ercole Biotech, Inc.

In May 2003, Isis and Ercole Biotech, Inc. ("Ercole") initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, the two parties cross-licensed their respective splicing-related intellectual property. Ercole received a license to Isis's Bcl-x molecule and certain of Isis' chemistry patents. During 2003, Isis advanced $500,000 in cash in exchange for a promissory note convertible into equity, pursuant to a qualified financing, as defined by the underlying agreement. Due to the uncertainty in ultimately realizing any value from the consideration paid, Isis expensed the payments during 2003, and included them in research and development expense on the accompanying consolidated statements of operations.

Antisense Therapeutics Ltd., Inc.

In December 2001, Isis licensed its compound, ISIS 107248, an antisense inhibitor, to Antisense Therapeutics, Ltd., Inc. ("ATL"), a publicly-traded company listed on the Australian Stock Exchange. Isis and ATL are participating in a five-year antisense drug discovery and development collaboration, under which ATL pays Isis research fees, reimbursing Isis for costs related to preclinical work on ISIS 107248, and may purchase drugs from Isis. In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expire in 2008. Isis valued its initial ownership at $2.8 million, and recognizes revenue on this amount over the term of the agreement. For the years ended December 31, 2003, 2002 and 2001, Isis recorded revenue of $811,000, $3.7 million and $46,000 respectively, related to this collaboration. As of December 31, 2003, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was approximately 11%. Isis' balance sheet at December 31, 2003 and 2002 includes a short-term investment at fair market value of $3.6 million and $1.5 million, respectively, related to this equity investment.

OncoGenex Technologies, Inc.

Pursuant to a November 2001 drug development collaboration, Isis agreed to co-develop and commercialize the anti-cancer antisense drug candidate, OGX-011, or ISIS 112989, with OncoGenex, a privately-held Canadian oncology-focused research and development company. Pursuant to a September 2003 drug development collaboration, Isis also agreed to license certain technology and collaborate on the initial development of the anti-cancer antisense drug candidate, OGX-225, a second-generation drug, with OncoGenex. Under the terms of the collaboration, during 2003 OncoGenex paid Isis an up-front fee and Isis acquired an ownership interest in OncoGenex of less than 10%. Isis recorded the upfront fee as revenue during 2003. Isis recorded no revenue from OncoGenex during 2002 and 2001.

Amgen

In December 2001, Isis entered into a three-year collaboration with Amgen, Inc. ("Amgen") to discover new antisense drugs. Amgen has the right to develop and commercialize antisense drugs

resulting from the collaboration. Under the terms of the agreement, Isis is entitled to receive milestone payments upon key clinical, research and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. During 2003 and 2002, Isis recorded revenue of $1.9 million and $3.6 million, respectively, related to progress research milestones under this drug discovery collaboration.

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly that has four key components:

First, Lilly purchased $75.0 million of Isis common stock at $18 per share.

Second, Isis licensed to Lilly rights to Affinitak, an antisense drug which Lilly is testing in a Phase III trial for the treatment of non-small cell lung cancer. Lilly paid Isis $25.0 million in up-front fees for Affinitak and reimbursed Isis for Isis' Affinitak development costs. During 2003, 2002 and 2001, Isis recorded revenue of $11.1 million, $31.9 million and $9.2 million, respectively, related to the reimbursement of Affinitak costs.

Third, Isis initiated with Lilly a four-year antisense drug discovery collaboration in the areas of metabolic and inflammatory diseases and a related collaboration to determine the function of up to 1,000 genes. In 2002, Lilly and Isis expanded this collaboration to include oncology and the license of LY2181308, formerly called ISIS 23722, Isis' antisense inhibitor of survivin, which is the first compound under the collaboration which Lilly has selected for clinical development. During 2003, Isis recorded revenue of $1.5 million under this collaboration related to a development milestone for LY2181308.

Fourth, Lilly committed to lend Isis, interest-free, up to $100.0 million over a four-year period to fund its obligations under the drug discovery collaboration. Isis can repay this loan at its option in either cash or Isis common stock, at a fixed conversion price of $40 per share. During 2003, 2002 and 2001, Isis recorded revenue related to the research collaboration loan of $7.5 million, $3.2 million, and $407,000, respectively and corresponding interest expense during 2003, 2002, and 2001, of $7.5 million, $3.2 million, and $407,000, respectively.

In September 2002, Isis further expanded its relationship with Lilly by agreeing to manufacture Affinitak during the product launch period for Lilly. In connection with this agreement, Isis upgraded and expanded its current manufacturing facility and added a new manufacturing suite. Lilly provided Isis with $21.2 million to build the new suite which Isis initially intended to use for the commercial manufacture of Affinitak. In June 2003, Lilly waived repayment of the $21.2 million manufacturing loan and agreed to allow Isis to use the facility to manufacture other drugs. In exchange, Isis released Lilly from its obligation to purchase additional product from Isis and its obligation to pay for the costs of maintaining an idle manufacturing suite.

Merck & Co., Inc.

In May 2001, Isis agreed to license to Merck & Co, Inc. ("Merck"), Isis' preclinical Type 2 diabetes antisense drug candidate, ISIS 113715. In exchange for the license, Isis received an upfront payment. In addition, Isis received development funding and earned a development milestone. During 2002 and 2001, Isis recorded revenue of $840,000 and $4.4 million, respectively, under this agreement. Isis reacquired full product rights to ISIS 113715 from Merck in December 2002. As a result, no revenue was recorded for the year ended December 31, 2003.

In June 1998, Isis entered into a research collaboration with Merck to discover small molecule drug candidates to treat patients infected with HCV. The collaboration, which concluded in May 2003 in accordance with its terms, provided that Merck would pay Isis' annual research support and milestone payments. Within the collaboration, Isis and Merck designed, synthesized, and evaluated novel compounds that Merck screened in its proprietary assays for identifying HCV replication inhibitors. Merck had the right to commercialize any drugs arising from the collaboration, and Isis retains the right to use technology developed in the collaboration in its antisense program. During 2003, 2002, and 2001, Isis recorded revenue of $900,000, $2.2 million and $3.6 million, respectively, from Merck under the terms of this agreement.

Elan Corporation

During 1999 and 2000, Isis and Elan, formed HepaSense, a joint venture to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus, or HCV, and Orasense, a joint venture to develop technology for the formulation of oral drugs. Isis and Elan provided development and manufacturing services to HepaSense and Orasense during the joint ventures through late 2002, when Elan concluded its participation in both collaborations. Isis regained all rights to ISIS 14803, the compound that HepaSense had been developing, and ISIS 104838, the compound Orasense had been developing. Isis has continued to develop its oral delivery technology initially developed within Orasense.

During 2002 and 2001, Isis recorded revenue of $3.0 million and $5.2 million, respectively, from HepaSense, and $8.9 million and $5.4 million, respectively, from Orasense, which Isis included in the consolidated statements of operations as research and development revenue from affiliates. Isis recorded no revenue from HepaSense or Orasense during 2003. During 2002 and 2001, Isis recorded $6.5 million and $8.3 million, respectively, as equity in the loss of HepaSense, and $9.5 million and $10.3 million, respectively, as equity in the loss of Orasense. There was no equity in the loss of HepaSense or Orasense during 2003. At December 31, 2002, the balance sheet included $6.2 million of contracts receivable relating to Orasense and a funding obligation due to Orasense of $5.2 million. Isis fully funded Orasense for this obligation in 2003 and Orasense paid Isis amounts due to it. As of December 31, 2003, Isis had no receivable or funding obligation related to Orasense.

Novartis Ophthalmics AG

In July 1997, Isis and Novartis Ophthalmics AG, ("Novartis"), formerly CIBA Vision Corporation, entered into an agreement granting Novartis exclusive worldwide distribution rights for Vitravene or fomivirsen. Under the terms of the agreement, Isis manufactures and sells Vitravene to Novartis, who is responsible for worldwide sales and marketing. During 2002, Isis recorded revenue of $2.5 million related to a milestone payment from Novartis, and $293,000 in revenue related to the shipment of Vitravene. Isis recorded no revenue related to the sales of Vitravene during 2003 and 2001.

Ibis Collaborations

Through its Ibis program, Isis continues to collaborate with San Diego-based Science Applications International Corporation, or SAIC, on a multi-year project funded by the Defense Advanced Research Projects Agency, or DARPA, for the ongoing development of Isis' Triangulation Identification for Genetic Evaluation of Risks ("TIGER") technology. This project combines Isis' expertise in microbial genome sequence analysis and advanced mass spectrometry technology with SAIC's advanced signal

processing capabilities. As of December 31, 2003, Isis had been awarded funding of $13.3 million related to this collaboration with SAIC, of which $13.3 million had been billed and $11.9 million had been collected.

In September 2003, Isis received a three-year grant for up to $6.0 million from the Centers for Disease Control, or CDC, to develop and apply its TIGER technology to the surveillance of human infectious disease in the U.S. Using the grant from the CDC, Isis expects to develop and provide TIGER technology for CDC projects focused on emerging human infectious disease.

In March 2004, Isis entered into a two-year contract with SAIC to further the development of Isis' TIGER biosensor to identify infectious agents in biological warfare attacks. The contract provides for up to $19.5 million in funding by DARPA.

Since inception, Isis has received financial support from government-funded grants and contracts to use its technology to assist in national defense. In March 2002, Isis transitioned its government-sponsored research program to discover novel broad-spectrum antibacterial drugs for biological warfare defense to the U.S. Army Medical Research Institute for Infectious Diseases, or USAMRIID. USAMRIID awarded Isis a three-year, $2.4 million contract to advance Isis' work in this area.

In addition to DARPA, USAMRIID and the CDC, Isis also has research relationships with other government entities including the United States Navy and the Federal Bureau of Investigation. During 2003, 2002, and 2001, Isis recorded revenue generated directly or indirectly from agencies of the U.S. Government of $9.5 million, $5.9 million, and $2.9 million, respectively.

Licensing Agreements

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., ("Eyetech"), a publicly-held company, certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense compound intended for use in the treatment of ophthalmic diseases. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis. In December 2002, Eyetech entered into an agreement with Pfizer to develop and commercialize Macugen. In 2003, Pfizer and Eyetech reported encouraging Phase III data for Macugen that Eyetech believes will serve as the basis for a new drug application with commercialization of the drug expected in 2005. Assuming successful commercialization of Macugen, Isis has the opportunity to earn future milestone payments and royalties.

IDT

In March 1999, Isis established a long-term research scale antisense inhibitor supply agreement with IDT, which provides for IDT to manufacture research scale antisense inhibitors and research reagents to Isis' specifications. Isis initially paid IDT $5.0 million toward future purchases of supplies and in December 2001 expanded its licensing agreement on certain antisense patents to allow Isis to exclusively sublicense these patents for functional genomics purposes. The agreement also eliminated milestone payments and reduced royalty rates Isis was to pay IDT for commercialized second-generation antisense drugs. In addition, Isis has paid IDT $350,000, $350,000, and $3.5 million in 2003, 2002 and 2001, respectively, and will pay IDT $700,000 over the next two years for the license. At December 31, 2003 and 2002, Isis' balance sheet reflected a deposit of $4.3 million and $4.5 million, respectively, and a licensing asset, net of amortization, of $4.2 million and $4.5 million, respectively.

Hybridon

Pursuant to a license agreement with Hybridon in May 2001 and amended August 2002, Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to Isis's suite of RNase H patents. Under the terms of the amended agreement, Isis paid Hybridon $15.0 million in cash and issued to Hybridon approximately 357,000 shares of Isis common stock valued at $5.0 million and 500,000 shares of Isis common stock valued at $10.0 million. Hybridon made a cash payment to Isis of $700,000 and issued to Isis approximately 1.0 million shares of its common stock valued at $1.3 million. Isis' balance sheet at December 31, 2003, 2002 and 2001 reflected a licensing asset, net of amortization, of $23.2 million, $25.1 million and $27.4 million, respectively, and a short-term investment at fair market value of $1.1 million and $704,000, respectively, related to this agreement.

7. Significant Customers and Concentration of Business Risk

A relatively small number of customers accounted for a significant percentage of Isis' revenue in the fiscal years ended December 31, 2003, 2002 and 2001. In 2003, 2002 and 2001, one significant customer accounted for approximately 62%, 57% and 27% of revenue, respectively. During 2003, Isis derived approximately 20% of its revenue directly or indirectly from agencies of the U.S. Government, including approximately 16% of revenue from one significant customer. Contract receivables from this customer comprised approximately 49% of contract receivables at December 31, 2003.

8. Restructuring

In April 2003, Isis initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, Isis had a small reduction in its workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, Isis incurred a

restructuring charge of approximately $1.8 million during the second quarter of 2003. Isis completed the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

In November 2002, Isis announced the termination of the GeneTrove database product offering and the resulting reorganization of the GeneTrove program. As a result, Isis reduced its workforce by approximately 25 people. The restructuring plan also provided for the write-down of certain intellectual property. As a result of this plan, Isis recognized restructuring related charges of approximately $1.4 million as operating expenses in the fourth quarter of 2002. Isis did not recognize any additional GeneTrove restructuring related charges for the year ended December 31, 2003 and completed utilization of the reserve related to this restructuring in the fourth quarter of 2003.

The following table summarizes the balance of the accrued restructuring reserve related to GeneTrove and Affinitak (in thousands):

	GeneTrove Severance Cost for Involuntary Employee Terminations	GeneTrove Write-Down of Intellectual Property	Affinitak Severance Cost for Involuntary Employee Terminations	Total
Balance at December 31, 2001	$ —	$ —	$ —	$ —
Reserve established	768	605	—	1,373
Utilization of reserves:				
Cash	(379)	—	—	(379)
Non-cash	—	(605)	—	(605)
Balance at December 31, 2002	$ 389	$ —	$ —	$ 389
Reserve established	—	—	1,803	1,803
Utilization of reserves:				
Cash	(389)	—	(1,803)	(2,192)
Non-cash	—	—	—	—
Balance at December 31, 2003	$ —	$ —	$ —	$ —

9. Employee Postemployment Benefits

Isis has an employee 401(k) salary deferral plan, covering all domestic employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($12,000 and $14,000 in 2003 for employees under 50 years old and over 50 years old, respectively). Isis made approximately $463,000 and $413,000 in matching contributions for the years ended December 31, 2003 and 2002, respectively.

10. Affiliate Supplementary Disclosure

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in Orasense under the equity method of accounting through 2002. At inception, Elan granted to Orasense a license to its intellectual property for $15.0 million. The term of the license was three years and amortization expense related to this license was $1.3 million for the year ended December 31, 2002. Through December 2002, Orasense incurred research and development expenses, performed by Elan and Isis on Orasense's behalf, in the course of its product development. In conjunction with its restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002. As a result, Isis regained all rights to ISIS 104838, the compound that Elan and Isis were developing within Orasense. Isis has continued to develop its oral delivery technology within Orasense.

The following table presents summary financial information for Orasense as of and for the years ended (in thousands, except per share amounts):

	December 31,	
	2003	2002
Balance Sheet:		
Assets		
Cash and cash equivalents	$ 6	$ 9
Total assets	$ 6	$ 9
Liabilities and Stockholders' Equity		
Amounts due to affiliates	$ —	$ 6,537
Common stock, $1.00 par value; 12,000 authorized, issued and outstanding at December 31,	12	12

2003 and 2002		
Additional paid-in capital	50,129	39,388
Accumulated deficit	(50,135)	(45,928)
Total liabilities and stockholders' equity	$ 6	$ 9
Results of Operations:		
Revenue	$ —	$ —
Research and development expenses	4,207	10,660
Amortization of acquired license	—	1,250
Total operating expenses	4,207	11,910
Net loss	$ (4,207)	$ (11,910)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in HepaSense under the equity method of accounting through 2002. At inception, Elan granted to HepaSense a license to its intellectual property for $15.0 million. The term of the license was 3 years and amortization expense related to this license totaled $5.0 million for the year ended December 31, 2002. HepaSense incurred research and development expenses, performed by Elan and Isis on HepaSense's behalf, in the course of its product development. In conjunction with its restructuring efforts, Elan concluded its participation in the HepaSense collaboration in 2002 and Isis regained all rights to ISIS 14803, the compound that Elan and Isis were developing within HepaSense. As a result of the collaboration termination, there was no activity during the year ended December 31, 2003.

The following table presents summary financial information for HepaSense as of and for the years ended (in thousands, except per share amounts):

	December 31,	
	2003	2002
Balance Sheet:		
Assets		
Cash and cash equivalents	$ 4	$ 4
Total assets	$ 4	$ 4
Liabilities and Stockholders' Equity		
Common stock, $1.00 par value; 6,001 shares authorized, issued and outstanding at December 31, 2003 and 2002	$ 6	$ 6
Series A Preferred stock, $1.00 par value; 6,000 shares authorized, issued and outstanding at December 31, 2003 and 2002	6	6
Additional paid-in capital	26,221	26,221
Accumulated deficit	(26,229)	(26,229)
Total liabilities and stockholders' equity	$ 4	$ 4
Results of Operations:		
Revenue	$ —	$ —
Research and development expenses	—	3,112
Amortization of acquired license	—	5,000
Total operating expenses	—	8,112
Net loss	$ —	$ (8,112)

11. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods.

Summarized quarterly data for the years ended December 31, 2003, and 2002 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2003 Quarters				
Revenues	$ 13,980	$ 15,017	$ 11,294	$ 9,699
Operating expenses	32,892	34,536	30,361	31,179
Loss from operations	(18,912)	(19,519)	(19,067)	(21,480)
Net loss	(24,321)	(23,097)	(22,203)	(25,375)
Accretion of dividends on preferred stock	(171)	(172)	(175)	(176)
Net loss applicable to common stock	$ (24,492)	$ (23,269)	$ (22,378)	$ (25,551)
Basic and diluted net loss per share(1)	$ (0.44)	$ (0.42)	$ (0.40)	$ (0.46)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2002 Quarters				
Revenues	$ 17,959	$ 20,061	$ 20,300	$ 21,859
Operating expenses	27,677	32,400	37,809	33,106
Loss from operations	(9,718)	(12,339)	(17,509)	(11,247)
Net loss	(17,972)	(20,865)	(17,576)	(15,829)
Accretion of dividends on preferred stock	(335)	(335)	(222)	(168)
Net loss applicable to common stock	$ (18,307)	$ (21,200)	$ (17,798)	$ (15,997)
Basic and diluted net loss per share(1)	$ (0.34)	$ (0.39)	$ (0.33)	$ (0.29)

(1) Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

12. Subsequent Events

DARPA Contract

In March 2004, Isis entered into a two-year contract with SAIC to further the development of Isis' TIGER biosensor to identify infectious agents in biological warfare attacks. The contract provides for up to $19.5 million in funding by DARPA.

Strategic Alliance with Alnylam

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. As part of the agreement, Isis also made a $10.0 million equity investment in Alnylam. In turn, Alnylam nonexclusively licensed Isis its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double stranded-RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either

an exclusive or co-exclusive basis depending on the target. If Isis develops or commercialize an RNAi-based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties.

QuickLinks

Exhibit 10.44

FINAL

LOAN AND SECURITY AGREEMENT

between

SILICON VALLEY BANK

and

ISIS PHARMACEUTICALS, INC.

December 15, 2003

$32,000,000

TABLE OF CONTENTS

This LOAN AND SECURITY AGREEMENT dated December 15, 2003, between SILICON VALLEY BANK ("Bank"), whose address is 3003 Tasman Drive, Santa Clara, California 95054 and ISIS PHARMACEUTICALS, INC. ("Borrower"), whose address is 2292 Faraday Avenue, Carlsbad, CA 92008, provides the terms on which Bank will lend to Borrower and Borrower will repay Bank. The parties agree as follows:

1. *ACCOUNTING AND OTHER TERMS.* Accounting terms not defined in this Agreement will be construed following GAAP. Calculations and determinations must be made following GAAP. The term "financial statements" includes the notes and schedules. The terms "including" and "includes" always mean "including (or includes) but not limited to," in this or any Loan Document.

2. *LOAN AND TERMS OF PAYMENT*

2.1 *Credit Extensions.*

Borrower will pay Bank the unpaid principal amount of all Credit Extensions and interest on the unpaid principal amount of the Credit Extensions.

2.1.1 Term Loan.

Bank will make a Term Loan available to Borrower in one advance.

2.2 *Reserved.*

2.3 *Interest Rate, Payments.*

(a) Interest Rate. The Term Loan accrues interest at a variable per annum rate equal to the greater of the Prime Rate or four percent (4.0%); provided that, on or before the Closing Date, Borrower may elect a fixed per annum rate of interest applicable to the Term Loan equal to the greater of the Treasury Note Rate or five and one quarter percent (5.25%); provided, further, that at any time after the Closing Date, Borrower may elect, by written notice to Bank received by 12:00 noon Pacific time on the day such rate is to be effective, a fixed per annum rate of interest applicable to the Term Loan equal to the then applicable variable rate plus one and one quarter (1.25) percentage points. In addition, at any time Borrower may reduce the applicable rate of interest on the Term Loan by one quarter (0.25) of a percentage point (up to a maximum of one half (0.50) of one percentage point) for each additional $25,000,000 in excess of the amount otherwise required hereunder that Borrower maintains in deposit and/or investment account balances at Bank or an affiliate of Bank. The variable rate of interest increases or decreases when the Prime Rate changes. After the occurrence and during the continuance of an Event of Default, Obligations accrue interest at two (2) percentage points above the rate effective immediately before the Event of Default. Interest is computed on a 360 day year for the actual number of days elapsed.

(b) Payments. Payments of principal and interest due on the Term Loan are payable on the 10th of each month. Borrower will pay 60 equal installments of principal and interest (the "Term Loan Payment"). Borrower's final Term Loan Payment, due on December , 2008, includes all outstanding Term Loan principal and accrued interest. Bank may debit any of Borrower's deposit accounts including Account Number 3300420522 for principal and interest payments owing or any other amounts due and payable by Borrower to Bank hereunder. Bank will promptly notify Borrower when it debits Borrower's accounts. These debits are not a set-off. Payments received after 12:00 noon Pacific time are considered received at the opening of business on the next Business Day. When a payment is due on a day that is not a Business Day, the payment is due the next Business Day and additional interest accrues.

(c) Prepayments. Borrower may prepay the Term Loan, in whole or in part, without penalty or premium so long as the Term Loan bears interest at a variable rate. If the Term Loan bears interest at a fixed rate as elected by Borrower hereunder, Borrower may prepay the Term Loan in whole only, and any such prepayment shall be made together with a prepayment fee equal to: (i) three percent (3%) of

---

the amount prepaid if prepayment is made during the first 16 months of the term of the Term Loan; (ii) two percent (2%) of the amount prepaid if prepayment is made during months 17 through 32 of the term of the Term Loan; (iii) one percent (1%) of the amount prepaid if prepayment is made during months 33 through 48 of the term of the Term Loan; and (iv) no prepayment fee shall be payable if prepayment is made after the fourth year of the term of the Term Loan.

2.4 *Fees.*

Borrower will pay:

(a) Bank Expenses. All Bank Expenses (including reasonable attorneys' fees and reasonable expenses) incurred through and after the date of this Agreement, are payable when due; provided, however, that these expenses will not exceed $15,000 so long as standard bank documents are used in this transaction.

(b) Loan Fee. On the Closing Date a loan fee equal to $75,000. The Parties acknowledge that Borrower has already paid Bank a $20,000 deposit which shall be applied against Bank Expenses and any balance shall be applied against the loan fee.

3. *CONDITIONS OF LOANS*

3.1 *Conditions Precedent to the Term Loan.*

Bank's obligation to make the Term Loan is subject to the following conditions precedent:

(a) Receipt by Bank of any Payment/Advance Form with respect to the funding of the Term Loan in its entirety.

(b) Receipt by Bank of evidence of repayment, or arrangement for repayment, of Borrower's debt owing to Boehringer Ingelheim and Elan.

(c) Execution and delivery by Borrower of a Negative Pledge Agreement, in form and substance attached hereto as Exhibit D, with respect to Borrower's Intellectual Property.

(d) Receipt by Bank of a legal opinion of Borrower's Vice President Legal and General Counsel in form and substance as attached hereto as Exhibit E.

(e) Borrower shall have established deposit and/or investment accounts at Bank or an affiliate of Bank with aggregate balances of at least the outstanding amount of the Term Loan.

(f) Satisfactory review by Bank of the subordination provisions of the indebtedness of Borrower in connection with its Convertible Subordinated Debt.

(g) The representations and warranties in Section 5 must be materially true and no Event of Default may have occurred and be continuing, or result from the Term Loan.

(h) Bank shall receive the financial projections, information, agreements, and documents it reasonably requires.

4. *CREATION OF SECURITY INTEREST*

4.1 *Grant of Security Interest.*

Borrower grants Bank a continuing security interest in all presently existing and later acquired Collateral to secure all Obligations and performance of each of Borrower's duties under the Loan Documents. Except for Permitted Liens, any security interest will be a first priority security interest in the Collateral. If this Agreement is terminated, Bank's lien and security interest in the Collateral will continue until Borrower fully satisfies its Obligations. At any time during the term hereof, if no Event of Default then exists, Borrower may elect to pledge to Bank a first priority security interest in a certificate of deposit (the "CD") in the principal amount of at least the amount of the then outstanding

balance under the Term Loan, and, upon such pledge, Bank agrees that it shall immediately release its security interest in all other Collateral and will amend this Agreement to release Borrower from the application of the covenants set forth in clause (ii) of Section 6.2(a), Sections 6.3 - 6.6, 6.8 - 6.10, 7.2 - 7.4, and 7.6 - 7.9. The CD shall thereafter constitute the sole Collateral for the remainder of the term of the Term Loan (including for purposes of the surviving covenants under Sections 7.1 and 7.5)) and shall be maintained at a balance at all times of at least the then outstanding amount of the Term Loan.

4.2 *Contingent Cash Collateral.*

In the event there is a breach by Borrower of the covenant set forth in Section 6.8, Borrower shall immediately pledge and deliver to Bank a CD in the principal amount of at least the amount of the then outstanding balance under the Term Loan. Such delivery and pledge of the CD shall be deemed to have cured the Event of Default arising from the breach of such covenant. If Borrower shall thereafter comply with the requirement of Section 6.8 hereunder and, subject to Borrower's option to pledge the CD under Section 4.1 hereunder in lieu of the other Collateral, if no other Event of Default shall exist, and if Bank shall at such time continue to hold a perfected, first priority security interest in the Collateral, then Bank shall release the CD to Borrower.

4.3 *Bank Account Collateral.*

Bank hereby agrees that so long as no Event of Default exists, except as provided in Section 4.1 with respect to the CD, Bank's security interest in any deposit or investment account shall not restrict Borrower's right to access and employ funds in such accounts. Bank further agrees that upon any exercise of its rights and remedies hereunder upon the occurrence and during the continuance of an Event of Default, Bank shall exercise such rights and remedies in the following order: (i) first as to deposit and investment accounts held at Bank or an affiliate of Bank, (ii) second as to any deposit or investment accounts held at third party financial institutions, and (iii) third as to any other Collateral secured under Section 4.1. In addition, Bank will not exercise its rights under any control agreements issued pursuant to Section 6.10 unless an Event of Default has occurred and is continuing.

5. *REPRESENTATIONS AND WARRANTIES*

Borrower represents and warrants as follows:

5.1 *Due Organization and Authorization.*

Borrower and each Subsidiary is duly existing and in good standing in its state of formation and qualified and licensed to do business in, and in good standing in, any state in which the conduct of its business or its ownership of property requires that it be qualified, except where the failure to do so could not reasonably be expected to cause a Material Adverse Change.

The execution, delivery and performance of the Loan Documents have been duly authorized, and do not conflict with Borrower's certificate of incorporation and bylaws, nor constitute an event of default under any Material Agreement by which Borrower is bound. Borrower is not in default under any agreement to which or by which it is bound in which the default could reasonably be expected to cause a Material Adverse Change.

5.2 *Collateral; Intellectual Property.*

Borrower has good title to the Collateral, free of Liens except Permitted Liens. The Accounts are bona fide, existing obligations, and the service or property has been performed or delivered to the account debtor or its agent for immediate shipment to and unconditional acceptance by the account debtor. To Borrower's knowledge, all Inventory is in all material respects of good and serviceable quality, free from material defects. Except as disclosed pursuant to Borrower's public filings with the Securities and Exchange Commission or as would not reasonably be expected to cause a Material

Adverse Change, Borrower owns, possesses, licenses or has other rights to use its Intellectual Property that is necessary for Borrower to conduct its business existing as of the Closing Date.

5.3 *Litigation.*

Except as shown in the Schedule, there are no actions or proceedings pending or, to the knowledge of Borrower's Responsible Officers and legal counsel, threatened by or against Borrower or any Subsidiary in which a likely adverse decision could reasonably be expected to cause a Material Adverse Change.

5.4 *No Material Adverse Change in Financial Statements.*

All consolidated financial statements for Borrower, and any Subsidiary, delivered to Bank fairly present in all material respects Borrower's consolidated financial condition and Borrower's consolidated results of operations. To Borrower's knowledge, there has not been any deterioration in Borrower's consolidated financial condition since the date of the most recent financial statements submitted to Bank that could reasonably be expected to cause a Material Adverse Change.

5.5 *Solvency.*

The fair salable value of Borrower's assets (including goodwill minus disposition costs) exceeds the fair value of its liabilities; the Borrower is not left with unreasonably small capital after the transactions in this Agreement; and Borrower is able to pay its debts (including trade debts) as they mature.

5.6 *Regulatory Compliance.*

Borrower is not an "investment company" or a company "controlled" by an "investment company" under the Investment Company Act. Borrower is not engaged as one of its important activities in extending credit for margin stock (under Regulations T and U of the Federal Reserve Board of Governors). Borrower has complied in all material respects with the Federal Fair Labor Standards Act. Borrower has not violated any laws, ordinances or rules, the violation of which could reasonably be expected to cause a Material Adverse Change. None of Borrower's or any Subsidiary's properties or assets has been used by Borrower or any Subsidiary or, to the best of Borrower's knowledge, by previous Persons, in disposing, producing, storing, treating, or transporting any hazardous substance other than legally or the violation of which would not cause a Material Adverse Change. Borrower and each Subsidiary has timely filed all required tax returns and paid, or made adequate provision to pay, all material taxes, except those being contested in good faith with adequate reserves under GAAP. Borrower and each Subsidiary has obtained all consents, approvals and authorizations of, made all declarations or filings with, and given all notices to, all government authorities that are necessary to continue its business as currently conducted, except where the failure to do so could not reasonably be expected to cause a Material Adverse Change.

5.7 *Subsidiaries.*

As of the Closing Date, Borrower does not own any stock, partnership interest or other equity securities except for Permitted Investments.

5.8 *Full Disclosure.*

No written representation, warranty or other statement of Borrower in any certificate or written statement given to Bank (taken together with all such written certificates and written statements to Bank) contains any untrue statement of a material fact or omits to state a material fact necessary to make the statements contained in the certificates or statements not misleading at the time such statement was made. It being recognized by Bank that the projections and forecasts provided by Borrower in good faith and based upon reasonable assumptions are not viewed as facts and that actual results during the period or periods covered by such projections and forecasts may differ from the projected and forecasted results.

---

6. *AFFIRMATIVE COVENANTS*

Borrower will do all of the following:

6.1 *Government Compliance.*

Borrower will maintain its and all Subsidiaries' legal existence and good standing in its jurisdiction of formation and maintain qualification in each jurisdiction in which the failure to so qualify would reasonably be expected to cause a Material Adverse Change. Borrower will comply, and have each Subsidiary comply, with all laws, ordinances and regulations to which it is subject, noncompliance with which could have a material adverse effect on Borrower's business or operations or would reasonably be expected to cause a Material Adverse Change.

6.2 *Financial Statements, Reports, Certificates.*

(a) Borrower will deliver to Bank: (i) within 5 Business Days of the required filing date, copies of all reports on Form 10-K, 10-Q and 8-K filed with the Securities and Exchange Commission; (ii) a prompt report of any legal actions pending against Borrower or any Subsidiary that could result in damages or costs to Borrower or any Subsidiary of $1,000,000 (to the extent not covered by insurance) or more; and (iii) budgets, sales projections, operating plans or other financial information which Borrower prepares in accordance with its past practices and which Bank reasonably requests.

(b) Within 5 Business Days of the required filing dates referenced in (a)(i) above with respect to reports on Form 10-K and 10-Q, Borrower will deliver to Bank a Compliance Certificate signed by a Responsible Officer in the form of Exhibit C.

6.3 *Inventory.*

Borrower will maintain its Inventory consistent with its past practices.

6.4 *Taxes.*

Borrower will make, and cause each Subsidiary to make, timely payment of all material federal, state, and local taxes or assessments.

6.5 *Insurance.*

Borrower will keep its business and the Collateral insured for risks and in amounts, as reasonable and customary for a corporation of similar size and business as Borrower. Insurance policies will be in a form, with companies, and in amounts that are reasonable and customary for a corporation of similar size and business as Borrower. All policies covering Collateral will have a lender's loss payable endorsement showing Bank as an additional loss payee and all liability policies covering Collateral will show the Bank as an additional insured. At Bank's request, Borrower will deliver certified copies of policies and evidence of all premium payments.

6.6 *Location of Equipment.*

Keep Borrower's and its Subsidiaries' Equipment only at the locations identified on Schedule 6.6 and their chief executive offices only at the locations identified on Schedule 6.6; provided, however, that Borrower may amend Schedule 6.6 so long as such amendment occurs by written notice to Bank not less than 30 days prior to the date on which such Equipment is moved to such new location or such chief executive office is relocated, so long as such new location is within the continental United States.

6.7 *Primary Accounts.*

On or before May 30, 2004, Borrower shall establish, and thereafter maintain, its primary depository and operating accounts with Bank; provided that prior to the funding of the Term Loan Borrower shall establish, and thereafter maintain, investment and deposit accounts at Bank or affiliates of Bank with aggregate balances at least equal to the outstanding amount of the Term Loan, and

provided further that between the Closing Date and May 30, 2004 Borrower shall use its best efforts to establish such other accounts with Bank. Such balances are not considered restricted.

6.8 *Financial Covenants.*

Borrower will maintain, as of the last day of each quarter, Liquidity of at least the greater of (a) Cash Burn for such quarter multiplied by two (2), or (b) the then outstanding balance of the Term Loan multiplied by one and one-half (1.5). "Liquidity" is unrestricted cash on hand (and cash equivalents). "Cash Burn" is the change in Liquidity from that as of the prior quarter end to Liquidity calculated at such quarter end, excluding such extraordinary items as Borrower may reasonably request and as Bank may approve in its reasonable discretion.

6.9 *Intellectual Property Rights.*

Borrower will protect, defend and maintain the validity and enforceability of its Intellectual Property to the extent necessary for Borrower to conduct its business.

6.10 *Control Agreements.*

With respect to deposit accounts or investment accounts maintained at financial institutions other than Bank (other than up to an aggregate of $1,000,000 maintained in financial institutions located outside of the United States), within the later of 5 Business Days of the opening of any such deposit account or investment account or 30 days after the Closing Date, Borrower will execute and deliver to Bank control agreements in form reasonably satisfactory to Bank in order for Bank to perfect its security interest in Borrower's deposit accounts or investment accounts; provided, however that with respect to any account maintained at an affiliate of Bank, such a control agreement shall be executed and delivered on or before the Closing Date.

6.11 *Further Assurances.*

Borrower will execute any further instruments and take further action as Bank reasonably requests to perfect or continue Bank's security interest in the Collateral or to effect the purposes of this Agreement.

7. *NEGATIVE COVENANTS*

Borrower will not do any of the following without Bank's prior written consent, which will not be unreasonably withheld or delayed:

7.1 *Dispositions.*

Convey, sell, lease, transfer or otherwise dispose of (collectively "Transfer"), or permit any of its Subsidiaries to Transfer, all or any part of the Collateral, other than (i) Transfers of Inventory in the ordinary course of business; (ii) Transfers of worn-out or obsolete Equipment; or (iii) other Transfers of Collateral in the ordinary course of business up to $5,000,000 per year but in no event including the CD.

7.2 *Changes in Business, Ownership, Management or Business Locations.*

Engage in or permit any of its Subsidiaries to engage in any business other than the businesses currently engaged in by Borrower or reasonably related or ancillary thereto or issue new equity securities in an amount greater than an aggregate of 33% of its common stock outstanding on the Closing Date, calculated on a fully diluted basis, in a single transaction or series of related transactions (unless such transactions are approved by Borrower's stockholders) or voluntarily terminate its Chief Executive Officer or Executive Vice President and Chief Financial Officer without cause.

7.3 *Mergers or Acquisitions.*

Merge or consolidate, or permit any of its Subsidiaries to merge or consolidate, with any other Person, or acquire, or permit any of its Subsidiaries to acquire, all or substantially all of the capital stock or property of another Person, except where (i) no Event of Default has occurred and is continuing or would result from such action during the term of this Agreement, (ii) Borrower is the surviving entity after any such transaction has been consummated and (iii) such transaction would not result in a decrease of more than 25% of Borrower's Tangible Net Worth. A Subsidiary may merge or consolidate into another Subsidiary or into Borrower. Notwithstanding the foregoing, Borrower may Transfer all or substantially all of its business to a Person (whether by merger, consolidation, sale of stock or sale of assets) if (i) such Person has a market capitalization or Tangible Net Worth equal to or greater than $500,000,000 immediately prior to the consummation of such transaction, and (ii) such Person assumes all rights, duties and obligations of Borrower under the Loan Documents.

7.4 *Indebtedness.*

Create, incur, assume, or be liable for any Indebtedness, or permit any Subsidiary to do so, other than Permitted Indebtedness.

7.5 *Encumbrance.*

Create, incur, or allow any Lien on any of the Collateral, or assign or convey any right to receive income, including the sale of any Accounts, or permit any of its Subsidiaries to do so, except for Permitted Liens, or permit any Collateral not to be subject to the first priority security interest granted here, subject to Permitted Liens.

7.6 *Distributions; Investments.*

Make any Investment in any Person, other than Permitted Investments, or permit any of its Subsidiaries to do so. Pay any dividends or make any distribution or payment or redeem, retire or purchase any capital stock, except for (i) repurchases of stock from former employees or directors of Borrower under the terms of applicable repurchase agreements in an aggregate amount not to exceed $5,000,000 in the aggregate in any fiscal year, (ii) redeeming, repaying or servicing Borrower's Convertible Subordinated Debt in accordance with the terms of such debt and (iii) redeeming or repaying the Lilly Debt in accordance with the terms of such debt, provided that no Event of Default has occurred, is continuing or would exist after giving effect to the repurchases.

7.7 *Transactions with Affiliates.*

Directly or indirectly enter into or permit any material transaction with any Affiliate except transactions that are in the ordinary course of Borrower's business, on terms less favorable to Borrower than would be obtained in an arm's length transaction with a non-affiliated Person.

7.8 *Subordinated Debt.*

Make or permit any payment on any Subordinated Debt, except under the terms of the Subordinated Debt, or amend any provision in any document relating to the Subordinated Debt that would reasonably be expected to cause a Material Adverse Change without Bank's prior written consent.

7.9 *Compliance.*

Become an "investment company" or a company controlled by an "investment company," under the Investment Company Act of 1940 or undertake as one of its important activities extending credit to purchase or carry margin stock, or use the proceeds of any Credit Extension for that purpose; fail to meet the minimum funding requirements of ERISA, permit a Reportable Event or Prohibited Transaction, as defined in ERISA, to occur; fail to comply with the Federal Fair Labor Standards Act

---

or violate any other law or regulation, if the violation could be expected to cause a Material Adverse Change, or permit any of its Subsidiaries to do so.

8. *EVENTS OF DEFAULT*

Any one of the following is an Event of Default:

8.1 *Payment Default.*

If Borrower fails to pay any of the Obligations within 5 Business Days after their due date. During the additional period the failure to cure the default is not an Event of Default (but no Credit Extension will be made during the cure period);

8.2 *Covenant Default.*

Subject to Section 4.1, If Borrower does not perform any obligation in Section 6 or violates any covenant in Section 7 or does not perform or observe any other material term, condition or covenant in this Agreement, or any other Loan Documents and as to any default under a term, condition or covenant that can be cured, and has not cured the default within 30 days of the earlier of written notice thereof from Bank or Borrower's actual knowledge thereof. During the additional time, the failure to cure the default is not an Event of Default (but no Credit Extensions will be made during the cure period);

8.3 *Material Adverse Change.*

If there occurs a Material Adverse Change, and if, in the determination of Bank (in its sole discretion), such Material Adverse Change is curable, Borrower has not cured the same within 30 days of the earlier of written notice thereof from Bank or Borrower's actual knowledge thereof. During the additional time, the failure to cure the default is not an Event of Default (but no Credit Extensions will be made during the cure period);

8.4 *Attachment.*

If any material portion of Borrower's assets is attached, seized, levied on, or comes into possession of a trustee or receiver and the attachment, seizure or levy is not removed in 10 days, or if Borrower is enjoined, restrained, or prevented by court order from conducting a material part of its business or if a judgment or other claim becomes a Lien on a material portion of Borrower's assets, or if a notice of lien, levy, or assessment is filed against any of Borrower's assets by any government agency and not paid within 10 days after Borrower receives notice. These are not Events of Default if stayed or if a bond is posted pending contest by Borrower (but no Credit Extensions will be made during the cure period);

8.5 *Insolvency.*

If Borrower becomes insolvent or if Borrower begins an Insolvency Proceeding or an Insolvency Proceeding is begun against Borrower and not dismissed or stayed within 30 days (but no Credit Extensions will be made before any Insolvency Proceeding is dismissed);

8.6 *Other Agreements.*

If there is a default in any agreement between Borrower and a third party that gives the third party the right to accelerate any Indebtedness exceeding $10,000,000 or that could cause a Material Adverse Change; provided that if such Indebtedness is owing by Borrower to a party who has entered into a technology collaboration or partnership agreement with Borrower, then such default shall be an Event of Default hereunder only if (i) such party accelerates such

Indebtedness, (ii) the accelerated amount of such Indebtedness exceeds $10,000,000, (iii) Borrower does not have the right to pay such accelerated Indebtedness through the issuance of its capital stock, and (iv) any cash payment of such

Indebtedness creates an Event of Default under this Agreement by breach of a financial or other covenant hereunder.

8.7 *Judgments.*

If a money judgment(s) in the aggregate of at least $5,000,000 (to the extent not covered by insurance) is rendered against Borrower and is unsatisfied and unstayed for 10 days (but no Credit Extensions will be made before the judgment is stayed or satisfied);

8.8 *Misrepresentations.*

If Borrower or any authorized Person acting for Borrower makes any material misrepresentation or material misstatement now or later in any warranty or representation in this Agreement, in any Loan Document, or in any writing delivered to Bank to induce Bank to enter this Agreement.

9. *BANK'S RIGHTS AND REMEDIES*

9.1 *Rights and Remedies.*

Subject to Section 4.3, When an Event of Default occurs and continues Bank may, without notice or demand, do any or all of the following:

(a) Declare all Obligations immediately due and payable (but if an Event of Default described in Section 8.5 occurs all Obligations are immediately due and payable without any action by Bank);

(b) Stop advancing money or extending credit for Borrower's benefit under this Agreement or under any other agreement between Borrower and Bank;

(c) Settle or adjust disputes and claims directly with account debtors for amounts, on terms and in any order that Bank considers advisable;

(d) Make any payments and do any acts it considers necessary or reasonable to protect its security interest in the Collateral. Borrower will assemble the Collateral if Bank requires and make it available as Bank designates. Bank may enter premises where the Collateral is located, take and maintain possession of any part of the Collateral, and pay, purchase, contest, or compromise any Lien which appears to be prior or superior to its security interest and pay all expenses incurred. Borrower grants Bank a license to enter and occupy any of its premises, without charge, to exercise any of Bank's rights or remedies;

(e) Apply to the Obligations any (i) balances and deposits of Borrower it holds, or (ii) amount held by Bank owing to or for the credit or the account of Borrower;

(f) Ship, reclaim, recover, store, finish, maintain, repair, prepare for sale, advertise for sale, and sell the Collateral. Bank is granted a non-exclusive, royalty-free license or other right to use, without charge, Borrower's Intellectual Property solely to extent required in completing production of, advertising for sale, and selling any Collateral and, in connection with Bank's exercise of its rights under this Section, Borrower's rights under all licenses and all franchise agreements inure to Bank's benefit; and

(g) Dispose of the Collateral according to the Code.

9.2 *Power of Attorney.*

Effective only when an Event of Default occurs and continues, Borrower irrevocably appoints Bank as its lawful attorney to: (i) endorse Borrower's name on any checks or other forms of payment or security; (ii) sign Borrower's name on any invoice or bill of lading for any Account or drafts against account debtors, (iii) make, settle, and adjust all claims under Borrower's insurance policies; (iv) settle and adjust disputes and claims about the Accounts directly with account debtors, for amounts and on terms Bank determines reasonable; and (v) transfer the Collateral into the name of Bank or a third

party as the Code permits, but only to the extent of the then current outstanding balance under the Term Loan. Bank may exercise the power of attorney to sign Borrower's name on any documents necessary to perfect or continue the perfection of any security interest regardless of whether an Event of Default has occurred, but only after Bank has requested in writing such actions from Borrower and Borrower has failed to promptly perform such action after such notice. Bank's appointment as Borrower's attorney in fact, and all of Bank's rights and powers, coupled with an interest, are irrevocable until all Obligations have been fully repaid and performed and Bank's obligation to provide Credit Extensions terminates.

9.3 *Accounts Collection.*

Subject to Section 4.3, when an Event of Default occurs and continues, Bank may notify any Person owing Borrower money of Bank's security interest in the funds and verify the amount of the Account. Borrower must collect all payments in trust for Bank and, if requested by Bank, immediately deliver the payments to Bank in the form received from the account debtor, with proper endorsements for deposit.

9.4 *Bank Expenses.*

If Borrower fails to pay any amount or furnish any required proof of payment to third persons, Bank may make all or part of the payment or obtain insurance policies required in Section 6.5, and take any action under the policies Bank deems prudent. Any amounts paid by Bank are Bank Expenses and immediately due

and payable, bearing interest at the then applicable rate and secured by the Collateral. No payments by Bank are deemed an agreement to make similar payments in the future or Bank's waiver of any Event of Default.

9.5 *Bank's Liability for Collateral.*

If Bank complies with reasonable banking practices and Section 9-207 of the Code, it is not liable for: (a) the safekeeping of the Collateral; (b) any loss or damage to the Collateral; (c) any diminution in the value of the Collateral; or (d) any act or default of any carrier, warehouseman, bailee, or other person. Borrower bears all risk of loss, damage or destruction of the Collateral.

9.6 *Remedies Cumulative.*

Bank's rights and remedies under this Agreement and the other Loan Documents are cumulative. Bank has all rights and remedies provided under the Code, by law, or in equity. Bank's exercise of one right or remedy is not an election, and Bank's waiver of any Event of Default is not a continuing waiver. Bank's delay is not a waiver, election, or acquiescence. No waiver is effective unless signed by Bank and then is only effective for the specific instance and purpose for which it was given. In all cases Bank's recourse under this Agreement is limited to the extent of the Obligations.

9.7 *Demand Waiver.*

Borrower waives demand, notice of default or dishonor, notice of payment and nonpayment, notice of any default, nonpayment at maturity, release, compromise, settlement, extension, or renewal of accounts, documents, instruments, chattel paper, and guarantees held by Bank on which Borrower is liable.

10. *NOTICES*

All notices or demands by any party about this Agreement or any other related agreement must be in writing and be personally delivered or sent by an overnight delivery service, by certified mail, postage prepaid, return receipt requested, or by telefacsimile to the addresses set forth at the beginning of this Agreement. A party may change its notice address by giving the other party written notice.

---

11. *CHOICE OF LAW, VENUE AND JURY TRIAL WAIVER*

California law governs the Loan Documents without regard to principles of conflicts of law. Borrower and Bank each submit to the exclusive jurisdiction of the State and Federal courts in Santa Clara County, California.

BORROWER AND BANK EACH WAIVE THEIR RIGHT TO A JURY TRIAL OF ANY CLAIM OR CAUSE OF ACTION ARISING OUT OF ANY OF THE LOAN DOCUMENTS OR ANY CONTEMPLATED TRANSACTION, INCLUDING CONTRACT, TORT, BREACH OF DUTY AND ALL OTHER CLAIMS. THIS WAIVER IS A MATERIAL INDUCEMENT FOR BOTH PARTIES TO ENTER INTO THIS AGREEMENT. EACH PARTY HAS REVIEWED THIS WAIVER WITH ITS COUNSEL.

12. *GENERAL PROVISIONS*

12.1 *Successors and Assigns.*

This Agreement binds and is for the benefit of the successors and permitted assigns of each party. Unless pursuant to a transaction permitted under Section 7.3, Borrower may not assign this Agreement or any rights under it without Bank's prior written consent which may be granted or withheld in Bank's discretion. Bank has the right, without the consent of or notice to Borrower, to sell, transfer, negotiate, or grant participation in all or any part of, or any interest in, Bank's obligations, rights and benefits under this Agreement; provided, however, that if no Event of Default has occurred and is continuing, Bank will not sell, Transfer, negotiate or grant participation in all or any part of, or any interest in, Bank's obligations, rights and benefits under this Agreement to any of Borrower's competitors.

12.2 *Indemnification.*

Borrower will indemnify, defend and hold harmless Bank and its officers, employees, and agents against: (a) all obligations, demands, claims, and liabilities asserted by any other party in connection with the transactions contemplated by the Loan Documents; and (b) all losses or reasonable Bank Expenses incurred, or paid by Bank from, following, or consequential to transactions between Bank and Borrower (including reasonable attorneys fees and expenses), except for losses caused by Bank's gross negligence or willful misconduct.

12.3 *Time of Essence.*

Time is of the essence for the performance of all obligations in this Agreement.

12.4 *Severability of Provision.*

Each provision of this Agreement is severable from every other provision in determining the enforceability of any provision.

12.5 *Amendments in Writing, Integration.*

All amendments to this Agreement must be in writing and signed by Borrower and Bank. This Agreement represents the entire agreement about this subject matter. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of this Agreement merge into and are superceded by this Agreement and the Loan Documents.

12.6 *Counterparts.*

This Agreement may be executed in any number of counterparts and by different parties on separate counterparts, each of which, when executed and delivered, are an original, and all taken together, constitute one Agreement.

12.7 *Survival.*

Subject to Section 4.1, all covenants, representations and warranties made in this Agreement continue in full force while any Obligations remain outstanding. The obligations of Borrower in Section 12.2 to indemnify Bank will survive until all statutes of limitations for actions that may be brought against Bank have run.

12.8 *Confidentiality.*

In handling any confidential information, Bank will exercise the same degree of care that it exercises for its own proprietary information, but disclosure of information may be made (i) to Bank's subsidiaries or Affiliates in connection with their business with Borrower, (ii) to prospective transferees or purchasers of any interest in the loans, but only pursuant to a confidentiality agreement, (iii) as required by law, regulation, subpoena, or other order, and (iv) as required in connection with Bank's examination or audit, but only pursuant to a confidentiality agreement. Confidential information does not include information that either: (a) is in the public domain or in Bank's possession when disclosed to Bank if not the result of Banks breach of this Agreement, or becomes part of the public domain after disclosure to Bank; or (b) is disclosed to Bank by a third party, if Bank does not know, after due inquiry, that the third party is prohibited from disclosing the information.

12.9 *Attorneys' Fees, Costs and Expenses.*

In any action or proceeding between Borrower and Bank arising out of the Loan Documents, the prevailing party will be entitled to recover its reasonable attorneys' fees and other reasonable costs and expenses incurred, in addition to any other relief to which it may be entitled.

13. *DEFINITIONS*

13.1 *Definitions.*

In this Agreement:

"**Accounts**" are all existing and later arising accounts, contract rights, and other obligations owed Borrower in connection with its sale or lease of goods (including licensing software and other technology) or provision of services, all credit insurance, guaranties, other security and all merchandise returned or reclaimed by Borrower and Borrower's Books relating to any of the foregoing.

"**Affiliate**" of a Person is a Person that owns or controls directly or indirectly the Person, any Person that controls or is controlled by or is under common control with the Person, and each of that Person's senior executive officers, directors, partners and, for any Person that is a limited liability company, that Person's managers and members.

"**Bank Expenses**" are all audit fees and expenses and reasonable costs and expenses (including reasonable attorneys' fees and expenses) for preparing, negotiating, administering, defending and enforcing the Loan Documents (including appeals or Insolvency Proceedings and as limited by Section 12.9).

"**Borrower's Books**" are all Borrower's books and records including ledgers, records regarding Borrower's assets or liabilities, the Collateral, business operations or financial condition and all computer programs or discs or any equipment containing the information.

"**Business Day**" is any day that is not a Saturday, Sunday or a day on which the Bank is closed.

"Cash Burn" is defined in Section 6.8.

"**Closing Date**" is the date of this Agreement.

"**Code**" is the California Uniform Commercial Code.

"**Collateral**" is the property described on *Exhibit A* (unless modified pursuant to Section 4.1).

"**Contingent Obligation**" is, for any Person, any direct or indirect liability, contingent or not, of that Person for (i) any indebtedness, lease, dividend, letter of credit or other obligation of another such as an obligation directly or indirectly guaranteed, endorsed, co-made, discounted or sold with recourse by that Person, or for which that Person is directly or indirectly liable; (ii) any obligations for undrawn letters of credit for the account of that Person; and (iii) all obligations from any interest rate, currency or commodity swap agreement, interest rate cap or collar agreement, or other agreement or arrangement designated to protect a Person against fluctuation in interest rates, currency exchange rates or commodity prices; but "Contingent Obligation" does not include endorsements in the ordinary course of business. The amount of a Contingent Obligation is the stated or determined amount of the primary obligation for which the Contingent Obligation is made or, if not determinable, the maximum reasonably anticipated liability for it determined by the Person in good faith; but the amount may not exceed the maximum of the obligations under the guarantee or other support arrangement.

"**Copyrights**" are all copyright rights, applications or registrations and like protections in each work or authorship or derivative work, whether published or not (whether or not it is a trade secret) now or later existing, created, acquired or held.

"**Convertible Subordinated Debt**" means Borrower's $5^{1}/_{2}$% Convertible Subordinated Notes due 2009.

"**Credit Extension**" is the Term Loan and any other extension of credit by Bank for Borrower's benefit.

"**Equipment**" is all present and future machinery, equipment, furniture, vehicles, tools and parts in which Borrower has any interest.

"**ERISA**" is the Employment Retirement Income Security Act of 1974, and its regulations.

"**GAAP**" is United States generally accepted accounting principles.

"**Indebtedness**" is (a) indebtedness for borrowed money or the deferred price of property or services, such as reimbursement and other obligations for surety bonds and letters of credit, (b) obligations evidenced by notes, bonds, debentures or similar instruments, (c) capital lease obligations and (d) Contingent Obligations.

"**Insolvency Proceeding**" are proceedings by or against any Person under the United States Bankruptcy Code, or any other bankruptcy or insolvency law, including assignments for the benefit of creditors, compositions, extensions generally with its creditors, or proceedings seeking reorganization, arrangement, or other relief.

"**Intellectual Property**" is:

(a) Copyrights, Trademarks, Patents, and Mask Works including amendments, renewals, extensions, and all licenses or other rights to use and all license fees and royalties from the use;

(b) Any trade secrets and any intellectual property rights in computer software and computer software products now or later existing, created, acquired or held;

(c) All design rights which may be available to Borrower now or later created, acquired or held;

(d) Any claims for damages (past, present or future) for infringement of any of the rights above, with the right, but not the obligation, to sue and collect damages for use or infringement of the intellectual property rights above; and

(e) All proceeds and products of the foregoing, including all insurance, indemnity or warranty payments.

"**Inventory**" is present and future inventory in which Borrower has any interest, including merchandise, raw materials, parts, supplies, packing and shipping materials, work in process and finished products intended for sale or lease or to be furnished under a contract of service, of every kind and description now or later owned by or in the custody or possession, actual or constructive, of Borrower, including inventory temporarily out of its custody or possession or in transit and including returns on any accounts or other proceeds (including insurance proceeds) from the sale or disposition of any of the foregoing and any documents of title.

"**Investment**" is any beneficial ownership of (including stock, partnership interest or other securities) any Person, or any loan, advance or capital contribution to any Person.

"**Lien**" is a mortgage, lien, deed of trust, charge, pledge, security interest or other encumbrance.

"**Liquidity**" is defined in Section 6.8.

"Lilly Debt" means the debt of the Borrower under that certain Loan Agreement dated August 17, 2001 between Borrower and Eli Lilly and Company.

"**Loan Documents**" are, collectively, this Agreement, any note, or notes or guaranties executed by Borrower, and any other present or future agreement between Borrower and/or for the benefit of Bank in connection with this Agreement, all as amended, extended or restated.

"**Mask Works**" are all mask works or similar rights available for the protection of semiconductor chips, now owned or later acquired.

"**Material Adverse Change**" means (i) a material adverse change in the business, operations, or financial condition of the Borrower; or (ii) a material impairment of the Borrower's ability to satisfy the Obligations; or (iii) a material impairment of the value or priority of Bank's security interests in the Collateral.

"**Material Agreement**" means an agreement to which Borrower is a Party that (i) Borrower has filed (including by incorporation by reference) as an exhibit to its annual report on Form 10-K or any of its quarterly reports on Form 10-Q during the fiscal year ending December 31, 2003 or (ii) Borrower entered into with Comerica Bank (including as successor to Comerica Bank-California and/or Imperial Bank) with respect to Borrower's real property.

"**Obligations**" are debts, principal, interest, Bank Expenses and other amounts Borrower owes Bank now or later under the Loan Documents, including cash management services, letters of credit and foreign exchange contracts, if any and including interest accruing after Insolvency Proceedings begin.

"**Patents**" are patents, patent applications and like protections, including improvements, divisions, continuations, renewals, reissues, extensions and continuations-in-part of the same.

"**Permitted Indebtedness**" is:

(a) Borrower's indebtedness to Bank under this Agreement or any other Loan Document;

(b) Indebtedness existing on the Closing Date and shown on the Schedule;

(c) Subordinated Debt;

(d) Indebtedness to trade creditors incurred in the ordinary course of business;

(e) Indebtedness secured by Permitted Liens; and

(f) Indebtedness other than Indebtedness described in clauses (a) through (e) of this definition of Permitted Indebtedness, provided such Indebtedness shall not exceed $5,000,000 in the aggregate at any given time; and

(g) extensions, refinancings and renewals of any items of Permitted Indebtedness.

"Permitted Investments" are:

(a) Investments shown on the Schedule and existing on the Closing Date;

(b) Investments in Borrower's Subsidiaries existing on the date hereof;

(c) Investments consisting of notes receivable of, or prepaid royalties and other credit extensions to, customers and suppliers who are not Affiliates, in the ordinary course of business;

(d) Investments, including newly formed or acquired Subsidiaries, not otherwise permitted under Section 7.6 which do not exceed $5,000,000 in the aggregate during the term of this Agreement;

(e) Acquisitions permitted under Section 7.3; and

(f) Investments in compliance with Borrower's Investment Policy, approved by the Audit Committee of Borrower's board of directors on September 21, 2000, or as otherwise approved by Borrower's board of directors.

"Permitted Liens" are:

(a) Liens existing on the Closing Date and shown on the Schedule or arising under this Agreement or other Loan Documents;

(b) Liens for taxes, fees, assessments or other government charges or levies, either not delinquent or being contested in good faith and for which Borrower maintains adequate reserves on its Books, *if* they have no priority over any of Bank's security interests;

(c) Purchase money Liens (i) on Equipment acquired or held by Borrower or its Subsidiaries incurred for financing the acquisition of the Equipment, or (ii) existing on equipment when acquired, *if* the Lien is confined to the property and improvements and the proceeds of the equipment;

(d) Licenses or sublicenses granted in the ordinary course of Borrower's business or approved by Borrower's board of directors;

(e) Leases or subleases granted in the ordinary course of Borrower's business, including in connection with Borrower's leased premises or leased property;

(f) Liens arising from judgments, decrees or attachments in circumstances not constituting an Event of Default under Section 8.4 or Section 8.7;

(g) Deposits in the ordinary course of business under worker's compensation, unemployment insurance, social security and other similar laws, or to secure the performance of bids, tenders or contracts (other than for the repayment of borrowed money) or to secure indemnity, performance or other similar bonds for the performance of bids, tenders or contracts (other than for the repayment of borrowed money) or to secure statutory obligations (other than liens arising under ERISA or environmental liens) or surety or appeal bonds, or to secure indemnity, performance or other similar bonds;

(h) Liens in favor of customs and revenue authorities arising as a matter of law to secure payments of custom duties in connection with the importation of goods;

(i) Liens of materialmen, mechanics, warehousemen, carriers, artisan's or other similar Liens arising in the ordinary course of Borrower's business or by operation of law, which are not past due or which are being contested in good faith by appropriate proceedings and for which reserves have been established in accordance with GAAP; and

(j) Liens incurred in the extension, renewal or refinancing of the indebtedness secured by Liens described in (a) through (i), *but* any extension, renewal or replacement Lien must be limited to the

property encumbered by the existing Lien and the principal amount of the indebtedness may not increase; provided that Borrower may extend or refinance its existing the indebtedness secured by Borrower's real property as of the Closing Date up to the appraised value of such real property.

"**Person**" is any individual, sole proprietorship, partnership, limited liability company, joint venture, company association, trust, unincorporated organization, association, corporation, institution, public benefit corporation, firm, joint stock company, estate, entity or government agency.

"**Prime Rate**" is Bank's most recently announced "prime rate," even if it is not Bank's lowest rate.

"**Responsible Officer**" is each of the Chief Executive Officer, the President, Executive Vice President, Chief Financial Officer and Vice President Finance.

"**Schedule**" is any attached schedule of exceptions.

"**Subordinated Debt**" is debt incurred by Borrower subordinated to Borrower's indebtedness owed to Bank on terms reasonably satisfactory to Bank.

"**Subsidiary**" is for any Person, or any other business entity of which more than 50% of the voting stock or other equity interests is owned or controlled, directly or indirectly, by the Person or one or more Affiliates of the Person.

"**Tangible Net Worth**" is, on any date, the consolidated total assets of Borrower and its Subsidiaries *minus*, without duplication, (i) any amounts attributable to (a) goodwill, (b) intangible items such as unamortized debt discount and expense, Patents, trade and service marks and names, Copyrights and research and development expenses except prepaid expenses, and (c) reserves not already deducted from assets, *and minus* (ii) Total Liabilities.

"**Term Loan**" is a loan of $32,000,000.

"**Term Loan Maturity Date**" is December 11, 2008.

"**Total Liabilities**" is on any day, obligations that should, under GAAP, be classified as liabilities on Borrower's consolidated balance sheet, including all Indebtedness, and current portion Subordinated Debt allowed to be paid, but excluding all other Subordinated Debt.

"**Trademarks**" are trademark and servicemark rights, registered or not, applications to register and registrations and like protections, and the entire goodwill of the business of Assignor connected with the trademarks.

"**Treasury Note Rate**" is, as of the Closing Date, the per annum rate of interest (based on a year of 360 days) equal to the sum of (a) the U.S. Treasury note yield to maturity for a term equal to 60 months as quoted in The Wall Street Journal, plus (b) 1.96 percentage points.

BORROWER:

ISIS PHARMACEUTICALS, INC.

By: _____

Title: _____

BANK:

SILICON VALLEY BANK

By: _____

Title: _____

EXHIBIT A

The Collateral consists of all of Borrower's right, title and interest in and to the following:

All goods and equipment now owned or hereafter acquired, including, without limitation, all machinery, fixtures, vehicles (including motor vehicles and trailers), and any interest in any of the foregoing, and all attachments, accessories, accessions, replacements, substitutions, additions, and improvements to any of the foregoing, wherever located;

All inventory, now owned or hereafter acquired, including, without limitation, all merchandise, raw materials, parts, supplies, packing and shipping materials, work in process and finished products including such inventory as is held for sale or lease, or to be furnished under a contract of service or is temporarily out of Borrower's custody or possession or in transit and including any returns or repossession upon any accounts or other proceeds, including insurance proceeds, resulting from the sale or disposition of any of the foregoing and any documents of title representing any of the above;

All contract rights and general intangibles now owned or hereafter acquired, including, without limitation, goodwill, leases, license agreements, franchise agreements, blueprints, drawings, purchase orders, customer lists, route lists, infringements, claims, computer programs, computer discs, computer tapes, literature, reports, catalogs, design rights, income tax refunds, payments of insurance, payment intangibles, and rights to payment of any kind;

All now existing and hereafter arising accounts (including health-care insurance receivables), contract rights, royalties, license rights and all other forms of obligations owing to Borrower arising out of the sale or lease of goods, the licensing of technology or the rendering of services by Borrower, whether or not earned by performance, and any and all credit insurance, guaranties, and other security therefor, as well as all merchandise returned to or reclaimed by Borrower;

All documents (including negotiable documents), cash, deposit accounts, securities, securities entitlements, securities accounts, investment property, financial assets, letters of credit, letter of credit rights, money, certificates of deposit, instruments (including promissory notes) and chattel paper (including tangible and electronic chattel paper) now owned or hereafter acquired and Borrower's Books relating to the foregoing;

All copyright rights, copyright applications, copyright registrations and like protections in each work of authorship and derivative work thereof, whether published or unpublished, now owned or hereafter acquired; all trade secret rights, including all rights to unpatented inventions, know-how, operating manuals, license rights and agreements and confidential information, now owned or hereafter acquired; all claims for damages by way of any past, present and future infringement of any of the foregoing; and

All Borrower's Books relating to the foregoing, and the computers and equipment containing said books and records, and any and all claims, rights and interests in any of the above and all substitutions for, additions and accessions to and proceeds thereof.

Notwithstanding the foregoing, the Collateral shall not be deemed to include any: (a) such property that (1) is nonassignable by its terms without the consent of the licensor thereof or another party (but only to the extent such prohibition on transfer is enforceable under applicable law, including, without limitation, Sections 9406 and 9408 of the Code), or (2) the granting of a security interest therein is contrary to applicable law, provided that upon the cessation of any such restriction or prohibition, such property shall automatically become part of the Collateral; (b) copyrights, copyright applications, copyright registration and like protection in each work of authorship and derivative work thereof, whether published or unpublished, now owned or hereafter acquired; any patents, patent applications and like protections including without limitation improvements, divisions, continuations, renewals, reissues, extensions and continuations-in-part of the same, trademarks, servicemarks and

applications therefor, whether registered or not, and the goodwill of the business of Borrower connected with and symbolized by such trademarks, any trade secret rights, including any rights to unpatented inventions, know-how, operating manuals, license rights and agreements and confidential information, now owned or hereafter acquired; or any claims for damage by way of any past, present and future infringement of any of the foregoing (collectively, the "Intellectual Property"), except that the Collateral shall include the proceeds of all the Intellectual Property that are accounts, (i.e. accounts receivable) of Borrower, or general intangibles consisting of rights to payment, if a judicial authority (including a U.S. Bankruptcy Court) holds that a security interest in the underlying Intellectual Property is necessary to have a security interest in such accounts and general intangibles of Borrower that are proceeds of the Intellectual Property, then the Collateral shall automatically, and effective as of the Closing Date, include the Intellectual Property to the extent necessary to permit perfection of Bank's security interest in such accounts and general intangibles of Borrower that are proceeds of the Intellectual Property; (c) interest in real property (including and any fixtures thereon, accessions thereto, and rents, issues and profits thereof); (d) any leased equipment or equipment owned by the United States government; or (e) any equity investment interest in subsidiaries, Orasense Ltd, Hepasense Ltd, Hybridon Inc., Antisense Therapeutics Limited (ATL), Ercole Biotech, Santaris Pharma A/S and Ocongenex Technologies Inc.

EXHIBIT B

LOAN PAYMENT/ADVANCE TELEPHONE REQUEST FORM

DEADLINE FOR SAME DAY PROCESSING IS 12:00 NOON., P.S.T.

TO: CENTRAL CLIENT SERVICE DIVISION DATE: _____

FAX #: (408) 496-2426 TIME: _____

FROM: ISIS PHARMACEUTICALS, INC.

CLIENT NAME (BORROWER)

REQUESTED BY: _____

AUTHORIZED SIGNER'S NAME

AUTHORIZED SIGNATURE: _____

PHONE NUMBER: _____

FROM ACCOUNT # _____ TO ACCOUNT # _____

REQUESTED TRANSACTION TYPE	**REQUESTED DOLLAR AMOUNT**
PRINCIPAL INCREASE (ADVANCE)	$
PRINCIPAL PAYMENT (ONLY)	$
INTEREST PAYMENT (ONLY)	$
PRINCIPAL AND INTEREST (PAYMENT)	$

OTHER INSTRUCTIONS: _____

All Borrower's representations and warranties in the Loan and Security Agreement are true, correct and complete in all material respects on the date of the telephone request for the Term Loan confirmed by this Borrowing Certificate; but those representations and warranties expressly referring to another date shall be true, correct and complete in all material respects as of that date.

BANK USE ONLY

TELEPHONE REQUEST:

The following person is authorized to request the loan payment transfer/loan advance on the advance designated account and is known to me.

Authorized Requester	Phone #
Received By (Bank)	Phone #

Authorized Signature (Bank)

EXHIBIT C
COMPLIANCE CERTIFICATE

TO: SILICON VALLEY BANK
3003 Tasman Drive
Santa Clara, CA 95054

FROM: ISIS PHARMACEUTICALS, INC.

The undersigned authorized officer of ISIS PHARMACEUTICALS, INC. ("Borrower"), certifies that under the terms and conditions of the Loan and Security Agreement between Borrower and Bank (the "Agreement"), (i) Borrower is in compliance for the period ending with all required covenants except as noted below and (ii) all representations and warranties in the Agreement are true and correct in all material respects on this date (except for those representations and warranties that expressly speak as of an earlier date, which continue to be true and correct in all material respects, in each case as of such earlier date). Attached are the required documents supporting the certification. The Officer certifies that these are prepared in accordance with U.S. Generally Accepted Accounting Principles (GAAP) consistently applied from one period to the next except as explained in an accompanying letter or footnotes. The Officer acknowledges that no borrowings may be requested at any time or date of determination that Borrower is not in compliance with any of the terms of the Agreement, and that compliance is determined not just at the date this certificate is delivered.

Please indicate compliance status by circling Yes/No under "Complies" column.

Reporting Covenant	Required	Complies	
10-Q, 10-K and 8-K	Within 5 days after required SEC filing date	Yes	No

Financial Covenant	Required		Actual	Complies	
Maintain on a Quarterly Basis:					
Minimum Liquidity	$	*	$	Yes	No

* Greater of 2 × Quarter's Cash Burn or 1.5 × Term Loan balance

Comments Regarding Exceptions: See Attached.

Sincerely,

Isis Pharmaceuticals, Inc.

SIGNATURE

TITLE

DATE

BANK USE ONLY

Received by:

AUTHORIZED SIGNER

Date:

Verified:

AUTHORIZED SIGNER

Date:

Compliance Status: Yes No

CORPORATE BORROWING RESOLUTION

Borrower: **Isis Pharmaceuticals, Inc.**
2292 Faraday Avenue
Carlsbad, CA 92008

Bank: **Silicon Valley Bank**
3003 Tasman Drive
Santa Clara, CA 95054-1191

I, the Secretary or Assistant Secretary of ISIS PHARMACEUTICALS, INC. ("Borrower"), CERTIFY that Borrower is a corporation existing under the laws of the State of Delaware.

I certify that at a meeting of Borrower's Directors (or by other authorized corporate action) duly held the following resolutions were adopted.

It is resolved that **any one** of the following officers of Borrower, whose name, title and signature is below:

NAMES	POSITIONS	ACTUAL SIGNATURES

may act for Borrower and:

Borrow Money. Borrow money from Silicon Valley Bank ("Bank").

Execute Loan Documents. Execute any loan documents Bank requires.

Grant Security. Grant Bank a security interest in any of Borrower's assets.

Negotiate Items. Negotiate or discount all drafts, trade acceptances, promissory notes, or other indebtedness in which Borrower has an interest and receive cash or otherwise use the proceeds.

Further Acts. Designate other individuals to request advances, pay fees and costs and execute other documents or agreements (including documents or agreement that waive Borrowers right to a jury trial) they think necessary to effectuate these Resolutions.

Further resolved that all acts authorized by these Resolutions and performed before they were adopted are ratified. These Resolutions remain in effect and Bank may rely on them until Bank receives written notice of their revocation.

I certify that the persons listed above are Borrower's officers with the titles and signatures shown following their names and that these resolutions have not been modified and are currently effective.

CERTIFIED TO AND ATTESTED BY:

X _____

*Secretary or Assistant Secretary

X _____

*NOTE: In case the Secretary or other certifying officer is designated by the foregoing resolutions as one of the signing officers, this resolution should also be signed by a second Officer or Director of Borrower.

EXHIBIT D

NEGATIVE PLEDGE AGREEMENT

NEGATIVE PLEDGE AGREEMENT

This Negative Pledge Agreement is made as of December 15, 2003, by and between Isis Pharmaceuticals, Inc. ("Borrower"), and Silicon Valley Bank ("Bank").

In connection with, among other documents, the Loan and Security Agreement (the "Loan Documents") being concurrently executed herewith between Borrower and Bank, Borrower agrees as follows:

ARTICLE I Except as otherwise permitted under the Loan Documents and except for (i) licenses or Transfers of Intellectual Property in the ordinary course of business and/or (ii) other licenses or Transfers of Intellectual Property that are approved by Borrower's board of directors, Borrower shall not sell, transfer, assign, mortgage, pledge, lease, grant a security interest in, or encumber any of Borrower's intellectual property, including, without limitation, the following:

1.1 Any and all copyright rights, copyright applications, copyright registrations and like protections in each work or authorship and derivative work thereof, whether published or unpublished and whether or not the same also constitutes a trade secret, now or hereafter existing, created, acquired or held;

1.2 All mask works or similar rights available for the protection of semiconductor chips, now owned or hereafter acquired;

1.3 Any and all trade secrets, and any and all intellectual property rights in computer software and computer software products now or hereafter existing, created, acquired or held;

1.4 Any and all design rights which may be available to Borrower now or hereafter existing, created, acquired or held;

1.5 All patents, patent applications and like protections including, without limitation, improvements, divisions, continuations, renewals, reissues, extensions and continuations-in-part of the same, including without limitation the patents and patent applications;

1.6 Any trademark and servicemark rights, whether registered or not, applications to register and registrations of the same and like protections, and the entire goodwill of the business of Borrower connected with and symbolized by such trademarks, including without limitation;

1.7 Any and all claims for damages by way of past, present and future infringements of any of the rights included above, with the right, but not the obligation, to sue for and collect such damages for said use or infringement of the intellectual property rights identified above;

1.8 All licenses or other rights to use any of the Copyrights, Patents, Trademarks or Mask Works, and all license fees and royalties arising from such use to the extent permitted by such license or rights; and

1.9 All amendments, extensions, renewals and extensions of any of the Copyrights, Trademarks, Patents, or Mask Works.

ARTICLE II It shall be an event of default under the Loan Documents between Borrower and Bank if there is a breach of any term of this Negative Pledge Agreement.

ARTICLE III Capitalized terms used but not otherwise defined herein shall have the same meaning as in the Loan Documents.

BORROWER:

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

Name: B. Lynne Parshall

Title: EVP and CFO

BANK:

SILICON VALLEY BANK

By: /s/ LINDA LE BEAU

Name: Linda Le Beau

Title: SVP

EXHIBIT E

OPINION OF COUNSEL

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 10.45

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.R.F §§ 200.80(B)4 AND 240.24B-2

EDB COY-15-RISC/I218-1
S03/1-1609901

31 October 2003

Ms B. Lynne Parshall, J.D.
Director
Isis Pharmaceuticals Singapore Pte Ltd
c/o Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008-7208
United States of America

Dear Lynne

APPLICATION FOR INCENTIVES UNDER THE RESEARCH INCENTIVE SCHEME FOR COMPANIES (RISC)

1 This is with reference to your application of 03/08/2003 and subsequent revisions for incentives under the Research Incentive Scheme for Companies (RISC).

2 We are pleased to inform you that the Economic Development Board (hereinafter called "the EDB") has agreed to provide a grant not exceeding [***] in total to ISIS PHARMACEUTICALS SINGAPORE PTE LTD (hereinafter called "the Company") under the RISC for your project on the development of ISIS R&D and SARS Programs (hereinafter called the "Development Project"), as described in your application. This grant shall be subject to the following conditions:

Project Implementation

(a) The Company shall implement the Development Project as indicated in the Company's application dated 03/08/2003 and subsequent revisions. The terms of the "Proposed Isis Singapore Program—1 September 2003" Term Sheet are accepted for this Development Project.

(b) The Development Project shall be carried out in 2 phases, where Phase One will be conducted in Isis Pharmaceuticals, Inc. facilities in the USA and Phase Two in the Company's facilities in Singapore.

(c) The Company shall meet the project milestones, deliverables and headcount commitment for Phase One and Two as shown in *Annex 1*. For Phase Two only, the Company shall not be obligated to reimburse the EDB for any grants that the Company has received, provided that the Company has made good faith efforts to substantially meet the milestones and deliverables as outlined in *Annex 1*.

Supported Period

(d) The Company shall complete the Development Project within the qualifying period, which shall be from **1 April 2003 to 31 August 2007**. **Specifically, the qualifying period for Phase One at Isis Pharmaceuticals, Inc.'s USA facilities shall be from 1 April 2003 to [***], and for Phase Two at the Company's R&D unit in Singapore (hereinafter referred to as "the R&D unit") will commence not later than [***], and for a total period of 3 years until 31 August 2007**. Only expenses incurred during this qualifying period will be supported except

---

that, it is anticipated that some Phase Two expenses (e.g. salary of the lab manager, expenses, such as equipment, associated with setting up of the R&D unit) will be incurred and supported in the effort to establish the R&D unit prior to the actual commencement of the Singapore facility. It is agreed that amortization of the equipment shall commence after the equipment is installed in the R&D unit. Expenses incurred outside the qualifying period will *not* be supported except as described above. The qualifying period shall not be extended to include any phases of the Development Project that were not originally included in the Company's application dated 03/08/2003.

Grant Support

(e) The grant shall cover actual qualifying costs for manpower, R&D equipment & materials and selected miscellaneous costs incurred by the Company on the Development Project during the qualifying period. The qualifying items of expenditures are listed below, but shall be subject to a total maximum grant of [***]. Virement of the grant from one cost category to another shall be permitted so long as the amount of funds changed does not exceed [***] of the category from which the funds are removed or [***] of the category into which funds are transferred. Virement of the grant from one cost category (manpower, equipment & material or professional services) to another for amounts greater than those allowed shall be considered on a case-by-case basis and shall require the prior approval of the EDB, which shall not be unreasonably withheld. Virement due to job title changes and changes in equipment are acceptable. Virement will not result in increase in grant funding.

(i) Phase One (carried out at Isis Pharmaceuticals, Inc.'s facilities in USA):

Cost Category	Cost Items	Approved Grant (S$)*
Manpower		

	Salary (Foreign)	[***]
Equipment & Material		
	Material / consumables	[***]
Professional services		
	Subcontract (Foreign)	[***]
Subtotal (Phase One)		[***]

(ii) Phase Two (carried out at the Company's R&D unit in Singapore)

Cost Category	Cost Items	Approved Grant (S$)*
Manpower		
	Salary (Local)	[***]
	Airfare	[***]
	Cost of living allowance	[***]
	Training	[***]
Equipment & Material		
	Equipment	[***]
	Material / consumables	[***]
Professional services		
	Subcontract (Local)	[***]
	Subcontract (Foreign)	[***]
Subtotal (Phase Two)		[***]
Total Approved Grant (Phase One + Phase Two)		[***]

* Please see *Annex 2* for details on qualifying costs.

(f) The qualifying cost for equipment (less its residual value, if any), is pro-rated based on the number of months equipment is used for the Development Project (this refers to the date of delivery to the end of qualifying period) over approved useful life of equipment (please see *Annex 2*). The useful life of equipment is as defined in the RISC grant application by the Company.

$$\text{Qualifying Cost} = (\text{Actual Expenses} - \text{Residual value}) \times \frac{\text{No. of months equipment is used for the project}}{\text{Approved useful life of equipment}}$$

(g) All equipment supported under this RISC grant shall be used exclusively for the Development Project. The Company shall not sell, dispose or otherwise transfer the R&D equipment to another party during the execution of the Development project without first obtaining the written approval of the EDB, which if so granted, shall be on such terms as the EDB deems fit. The Company shall at all times maintain proper records with respect to the assets acquired through the grant.

(h) The Company shall not seek or receive funds from any other incentives offered by other agencies of the Government of Singapore for funding of this Development Project.

(i) All grant monies received shall be used solely for the implementation of this Development project.

Disbursements for Phase One

(j) The 3 Phase One payments of [***] each are triggered by:

(i) Completion of [***]

(ii) Completion of [***]

(iii) Completion of [***]

Payments will be made within [***] working days after receipt of the complete claim documents by the EDB. If the claims have raised a question or concern, the EDB shall inform the Company in writing within such [***] working day period, specifying such question or concern. In such event, the [***] day working time limit shall cease to run and shall resume when the question or concern has been resolved.

Disbursements for Phase Two

(k) Disbursements may be made on a reimbursement basis upon application by the Company at quarterly intervals, subject to the fulfillment of paragraph 2(s) condition (1). Claims must be submitted using the prescribed *Form 1a and 1b* and shall be certified by the Company's Vice President of Finance and the Principal Investigator. The amount disbursed shall be based on the qualifying component of actual costs incurred.

The grant will be disbursed as follows:

(i) Disbursements of up to a cumulative total [***]% of the approved grant amount shall be made upon application by the Company.

(ii) The remaining [***]% of the grant may be released upon application by the Company on completion of the Development Project.

(l) For all claims (except for the final claim), the first [***]% of the amount claimed will be disbursed to the Company upon receipt of claim and the remaining [***]% will be disbursed upon the completion of checks, which in any event must be completed within [***]working days after receipt of the complete claim documents, and provided that the Company has been making regular quarterly claims so that any one claim is not unusually large which would require a protracted checking period to process. If the checks have raised a question or

---

concern, the EDB shall inform the Company in writing within such [***] working day period, specifying such question or concern. In such event, the [***] day working time limit shall cease to run and shall resume when the question or concern has been resolved.

(m) The final claim must be submitted within [***] months **with complete documentation** from the date of the offer letter / from the end of the development period (31 August 2007), **failing which any claim will be disqualified**.

Submission of Auditor's Statements & Progress Reports

Auditor's Statements

(n) **For total approved grant exceeding [***], all claims must be externally audited. This applies to the claims for *Phase Two* of the Development Project only.** (The EDB has waived the requirement for external auditors' certifications of ISIS USA Phase One claims of [***].) The audited statement of accounts shall be submitted on an **annual basis**, as well as when the Development Project is completed or terminated. The wording of the audited statement should follow the prescribed format in *Annex 6*. The Company shall make available to its auditor this Letter of Offer and its accompanying annexes as well as the attached Terms of Reference for the External Auditor per *Annex 7*. The Company shall ensure that the external auditor forwards a copy of the audited accounts directly to the EDB upon completion of the audit. In the event that the external auditor cannot issue an unqualified report, the EDB shall have direct access to the external auditor to gather details with regard to the audit findings.

Progress Reports/Final Report

(o) The Company shall submit progress reports to the EDB **after each milestone completion for Phase One, and at half-yearly intervals for Phase Two**, in accordance with the prescribed format in *Annex 8*. The disbursement of any grant shall be subject to the Company achieving the project milestones as stated in Paragraph 2(j) above and Annex 1. The final report is to be submitted upon full completion of the project.

Project Management & Co-ordination

(p) The Company shall appoint a person (hereinafter called the "Principal Investigator") to lead the Development Project. The Principal Investigator shall be responsible for the proper management, co-ordination and progress of the Development Project, the management of grants disbursed and all other matters pertaining to the Development Project, including the preparation of claims, submission of audited statements and progress reports.

(q) The Principal Investigator shall be deemed as an agent of the Company throughout the Development Project and the EDB shall at all times have access to the Principal Investigator with regards to all matters pertaining to the Development Project.

(r) The Company shall inform the EDB in writing of any change in the Principal Investigator.

Other Conditions

(s) This RISC grant is also subjected to the following conditions:

(1) Isis Pharmaceuticals, Inc. will set up the Company's R&D unit and commence implementation of Phase Two of the Development Project no later than [***] or within [***] days of lab space availability, whichever is later.

(2) In the event of successful commercialization of the SARS drug candidate(s) by Isis Pharmaceuticals, Inc., the Company or through 3rd party licensing, EDB will recoup [***], either via a percentage of sales or royalties (not exceeding [***].

---

(3) Both Isis Pharmaceuticals, Inc. and the EDB intend that Isis Pharmaceuticals, Inc. will establish the Company's R&D unit as per paragraph 2(s) condition (1) above. Both Isis Pharmaceuticals, Inc. and the EDB agree to certain remedies in the case that Isis Pharmaceuticals, Inc. fails to establish the Company's R&D unit either through its own decision or due to the failure of the EDB to provide the agreed-to fully fitted out laboratory space. These remedies are described as follows:

i. If the EDB fails to make available the agreed-to fully fitted out laboratory space by [***], Isis Pharmaceuticals, Inc. or the Company will have no obligation to [***]. Even in this event, Isis Pharmaceuticals, Inc. remains committed to establish the

Company's R&D unit as soon as practically possible.

ii. If Isis Pharmaceuticals, Inc. decides on its own to not proceed with establishing the Company's R&D unit even if the EDB has met its obligation to make fully fitted out laboratory space available, Isis Pharmaceuticals, Inc. agrees to either repay [***] to the EDB or provide to the EDB up to [***] times the actual grant provided to Isis Pharmaceuticals, Inc. or the Company [***] via a percentage of sales or royalties (not exceeding [***]) in the event of successful commercialization of the SARS drug candidate(s). The selection of the repayment mechanism is at the choice of the EDB.

(4) If Isis Pharmaceuticals, Inc. or the Company (as the case may be) decides to [***], on terms to be negotiated at that stage

(5) If no additional partners participate in funding the SARS drug(s), the [***]

(6) If additional partners are involved in funding, EDB or its Designee shall receive rights of negotiation and terms for Asia-Pacific (including Japan) that are comparable to the other partners.

(7) Isis Pharmaceuticals, Inc. will recruit and initiate training of at least [***] Isis Singapore researcher to lead the Company's operation in Singapore no later than [***].

(8) The manager/head of the Company will be employed by Isis Pharmaceuticals, Inc. and will devote [***] of his time for the Company's activities and spend approximately [***]% of his time in the USA

(9) Isis Pharmaceuticals, Inc. will recruit and initiate training of at least [***] researchers for the Company during 2004

(10) The Company will hire at least [***] full time employees (FTEs) in total (including [***] PhDs) no later than the end of 2005.

(11) The Company will incur total cumulative research spending of at least [***]) (inclusive of EDB's grant support) by the [***] anniversary of the establishment of the Company's R&D unit.

(12) The Company will undertake at least [***] disease programs besides SARS

(13) The Company will screen, identify and develop at least [***] SARS drug candidate up to [***] by the [***]anniversary of the establishment of the R&D unit.

(14) If Isis Pharmaceuticals, Inc. decides to spin-off or out-license drug candidate(s) arising from the Company, Isis Pharmaceuticals, Inc. will [***.]

(t) Isis Pharmaceuticals, Inc. and the Company shall permit EDB officers to inspect the premises where the development work is carried out, all accounts on the development expenditures and all records on the progress of the Development Project.

(u) The Company shall be required to provide, through responses to surveys or any other such studies carried out by the EDB, relevant information on the Development Project, as and when requested by the EDB subject to limitations of company confidential information and all

---

legal requirements and limitations concerning disclosure of confidential information considered to be material by the corporation.

3 In the event the Project is aborted, the Company is to inform EDB in writing immediately.

4 The EDB reserves the right to recover from the Company the total amount of grant disbursed to the Company in Phase Two in any calendar quarter for any breach of condition under which the RISC grant was approved. Prior to the recovery of the grant, the EDB will meet with the Company to discuss the matter. The parties will attempt to reach a solution that is mutually acceptable. If the parties are unable to arrive at a mutually acceptable solution, the EDB shall have the final decision on the matter.

5 The Company shall keep the terms and conditions of this RISC grant confidential. Such information shall not be released to any external party, the public or the press unless prior written consent from the EDB is given. Notwithstanding the foregoing, the Company shall be allowed to disclose the RISC grant information to the US Government and regulatory bodies when it is mandated by law. Where disclosures have to be made available to the public or the company's shareholders, the extent of such disclosure shall not extend to actual financial support granted to the company. Nevertheless, where it is mandated by law that the actual financial support amounts be disclosed to the shareholders of the company, the company undertakes to reasonably ensure that the recipients of such information are aware of the confidential and sensitive nature of such information and to take the necessary precautions against information leakage.

6 The EDB reserves the right to change the terms and conditions of this offer from time to time as may be specified and deemed necessary by the EDB.

7 If you are prepared to accept this offer of a grant under the conditions stipulated above, please sign the acceptance letter attached and return it to EDB within *1 month* from the date of this letter, **failing which this offer shall be deemed to have lapsed**.

8 If you have any queries, please contact Ms Tricia Huang at (65)-6832-6856. For queries on claims, please call the EDAS hotline at (65)-6832-6416. We wish you every success in this project.

Yours sincerely

/s/ BEH SWAN GIN

DR BEH SWAN GIN
DIRECTOR

BIOMEDICAL SCIENCES

Enc

Enclosures:

Acceptance Letter

Annex 1	Project Milestones and Deliverables
Annex 2	Details on Qualifying Costs
Annex 3	Submission of Claim Forms and Reports Form 1 a—Fund Request Form 1 b—Breakdown of Fund Request Form 1 c—Interbank Giro Form
Annex 4	Explanatory Notes on Qualifying Costs Categories for Research Incentive Scheme for Companies
Annex 4A	Checklist of commonly made errors
Annex 5	Sample Fund Request
Annex 6	Format for External Auditor's Statement
Annex 7	Terms of Reference for External Auditors
Annex 8	Format for Project Progress and Final Report

EDB COY-15-RISC/I218-1
S03/1-1609901

Date :

Chairman
Economic Development Board
250 North Bridge Road
#24-00 Raffles City Tower
Singapore 179101

Attention: Dr Beh Swan Gin

ACCEPTANCE OF GRANT AWARD UNDER THE RESEARCH INCENTIVE SCHEME FOR COMPANIES

1 I refer to your letter of offer dated 31 October 2003.

2 I confirm that my company will be undertaking the development project as submitted to the Board dated 03/08/2003 and subsequent revisions and that we accept the award of your grant not exceeding [***] in aggregate, subject to the terms and conditions set out in the above mentioned letter of offer.

3 We understand the need for EDB to ensure good governance of public fund and hence will do our utmost diligence in ensuring that all claims for reimbursement of project expenditure are true and correct and all offer letter terms and conditions are complied with.

Signature :

Stanley Crooke, Chairman of the Board, President and CEO

Signature :

Lynne Parshall, Director, EVP & CFO

Company Stamp :

ISIS Pharmaceuticals

Date :

Annex 1

Annex 2

[***]

Annex 3

SUBMISSION OF CLAIM FORMS & REPORTS FOR RISC GRANTS

Claims

Quarterly	—	Form 1a—Fund Request Form 1b—Breakdown of Fund Request Form 1c—Interbank Giro Form*
Yearly	—	Statement from Coy's external auditor (ref. Sample statement in Annex 6)

* To be submitted together with the first fund request. However, this is not necessary if you have already submitted the application to EDB earlier and there is no change in the bank details.

Report Submission

Half-Yearly	—	Project Progress Report (ref. Annex 8)
End of Project	—	Project Final Report (ref. Annex 8)

Form 1a

[***]

Form 1b

[***]

Form 1c

APPLICATION FORM FOR INTERBANK GIRO
Please complete Part A and get your bank to complete Part B before returning the ORIGINAL copy to the following address

ECONOMIC DEVELOPMENT BOARD
250 North Bridge Road #18-00
Raffles City Tower
Singapore 179101
Attention:

PART A (TO BE COMPLETED BY VENDOR)

1. Our bank details are as follows:

Account Name _____

Account Number _____

Bank Name and Branch _____

Bank Code and Branch Code _____

2. We authorise ECONOMIC DEVELOPMENT BOARD to credit all monies due to us this bank account. Amounts so discharged would constitute valid discharge of obligations due to us. This authorisation shall continue to be in force until we have revoked it by notice in writing delivered to you.

3. In the event of a change of bank account, we shall inform you in writing 30 days in advance before the change.

Signature of Authorised Personnel _____

Name and Designation _____

Company Stamp

Tel No and Fax No

Date

PART A (TO BE COMPLETED BY VENDOR'S BANK)

We certify that the bank details and the signatures affixed in PART A are correct and consistent with our records. Please initial against any amendments to the information contained in Part A.

Signature of Authorised Personnel

Name and Designation

Bank Stamp

Tel No and Fax No

Date

[***]

* Related parties will include all subsidiaries, associates and the parent company, as well as all parties defined by SAS 21 on Related Party Disclosures.

Annex 4

[***]

Annex 4A

[***]

Annex 5

[***]

Annex 6

Format for External Auditor's Statement

The Managing Director
Economic Development Board
250 North Bridge Road
#24-00 Raffles City Tower
Singapore 179101

We have performed the procedures as per the Terms of Reference on the Statement of Expenditure incurred by (name of company). This is in connection with the development of (project name or description and reference number) under the (name of grant/scheme) of the Economic Development Board ("EDB") for the qualifying period from (date) to (date). Our engagement was undertaken in accordance with the Singapore Standard on Auditing applicable to agreed upon procedure engagements.

The procedures were performed solely to assist you in evaluating whether the amounts shown on the attached statement are in accordance with the documents and records kept by the Company and whether those amounts have been included in accordance with the terms and conditions specified by the EDB in their Offer Letter dated (and Supplemental Offer Letters dated)*.

We report our findings below:

(a) With respect to item 1 of the Terms of Reference, we found no exceptions for procedures (a) to (h), and ensured that such procedures cover at least 85% of the value claimed in the statement.

(b) With respect to item 2 of the Terms of Reference, we found that related party claims are excluded from item categories that prohibit related party transactions.

(c) With respect to item 3 of the Terms of Reference, we found no sale/lease/transfer/disposal of equipment that is funded by EDB during the execution of the project.

(d) With respect to item 4 of the Terms of Reference, we found no going concern issues based on the latest audit report of the company

(Detail the exceptions if any)

Our report is solely for the purpose set forth in the second paragraph of this report and for your information, and is not to be used for any other purpose or to be distributed to any other parties. This report relates only to the accounts and items specified above and does not extend to any financial statements of (name of company), taken as a whole.

(firm)

Certified Public Accountants

Singapore

(date)

Annex 7

Terms of Reference for External Auditors

1) Verify that:

a) Items and amount claimed are in accordance with Annex 2 (Details on Qualifying Costs) and the terms and conditions of the offer letter (and supplemental offer letters, if any).

b) Items claimed are used for the sole purpose of the project as stated in the offer letter, unless otherwise stated.

b) Items claimed by the company are accurately recorded in all the claim forms and schedules, and in accordance with the books and records maintained by the company.

c) Description and authenticity of items claimed are valid based on review of appropriate source documents and other appropriate audit procedures.

d) Claims agree to the appropriate source documents, e.g. invoices, personnel and payroll records, etc.

e) Claims are made only upon disbursement of cash by the grant recipient, and do not include those that are purely accounting entries without cash outlays (e.g. accruals, depreciation).

f) All items claimed are incurred and paid within the qualifying period as per the terms and conditions of the offer letter (and supplemental offer letters, if any).

Exception:

For final claims, items claimed may be paid after the qualifying period, but before date of audit report.

g) Equipment claimed does exist through physical verification and are installed/operating during the period stipulated in the grant.

The procedures as listed above from (a) to (h) should cover at least 85% of the value claimed in the statement.

2) Verify that related party claims are excluded from item categories that prohibit related party transactions

3) Enquire and report on any sale/lease/transfer/disposal of the equipment, if applicable, that is funded by EDB during the execution of the project.

4) The auditors shall highlight any going concern issues raised in the latest audit report of the company

5) In the event that there are errors and deviations found, the auditors shall report accordingly and provide details.

Annex 8

FORMAT FOR PROGRESS/FINAL REPORT

Please submit a report of 5-10 pages in length using the following format:

Progress/Final* Report for the period to .

Project No.: Project Title:

Principal Party: **Principal Investigator:**

Secondary Party:

Project Commencement Date: **Project Completion Date:**

* Please delete accordingly

1 ***SUMMARY OF PROJECT STATUS***

1.1 Project Implementation Schedule

Please update the project implementation schedule—planned versus actual, and indicate in the remarks column, the reasons for any deviation.

	Implementation Schedule											
												Remarks
Capabilities	**1999**				**2000**				**2001**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Task A • Job I • Job II												
{Actual Implementation}												
Task B • Job I • Job II												
{Actual Implementation}												
Task C • Job I • Job II												
{Actual Implementation}												

original schedule as in Letter of Offer, Annex 1 — Project Deliverable & Milestones
actual schedule to-date

1.2 Highlight any *significant findings*, *noteworthy developments*, *milestones achieved* and *capability developed* in the course of the Project.

1.3 Comment on the reasons for any delay/deviation from planned project schedule.

The following are relevant only to reports for projects in progress:

1.4 Highlight with reasons any change in ownership, change in principal investigator or major change in business conditions that will have an impact on the Project.

1.5 Highlight any problems encountered that will impact on the future progress of the project.

1.6 Describe briefly your *plan of action for the next six months*, including remedial actions to overcome the problems encountered highlighted in 1.5 (if relevant).

---

2 ***R&D MANPOWER STATUS***

		1999	**2000**	**2001**	**Total**
No. of new RSEs(1) hired (cumulative):	*Committed(4)*				
	Actual				
No. of new non-RSEs(2) hired (cumulative):	*Committed*				
	Actual				
No. of existing(3) RSEs (cumulative):	*Committed*				
	Actual				
No. of existing non-RSEs hired (cumulative):	*Committed*				
	Actual				

Name of Researchers:
1.
2.

(1) RSE : *Researcher with Bachelor degree and above.*
(2) Non-RSE : *Researcher with diplomas qualification.*
(3) Existing : *Employed by the company before commencement of Project.*
(4) Committed : *Figures as originally stated in Letter of Offer, Annex I*

3 ***CUMULATIVE R&D RESULTS***

Please provide information where applicable. This information should be **cumulative.** For progress reports, information should be **updated**during **every half-yearly** report submission.

3.1

Capability Development

Year	Technologies/Capabilities Developed
1999	
2000	
2001	

3.2 Patents and Intellectual Properties Arising from the Project

Patents/Intellectual Properties	Date and Place Filed/Granted/Generated	Status
1. {Title} & {Patent No.}		
2. {Title} & {Patent No.}		
3. {Title} & {Patent No.}		

3.3 Commercialization of R&D Results

Year	New Products/Services Commercialized as a result of the R&D Project	Incremental Capital Investment(5) (S$)	Type of Activity(6)	No. of New Employment(7)
1999				
2000				
2001				

(5) Additional capital investments by the Singapore office as a result of the new activities.

(6) Type of activity in the value chain for the new product and/or service resulting from the R&D Project. E.g. manufacturing, marketing & distribution, technical support, sales, etc.

(7) No. of new jobs created as a result of the new activities.

3.4 Other Benefits to Company due to R&D Project

Benefits		1999	2000	2001	200...	200...
Revenue(8) attributed to the R&D Project (S$)	*Committed(4)*					
	Actual / Latest Forecast(9)					
Market share (%)	*Committed*					
	Actual / Latest Forecast					
Value-add per worker (S$)	*Committed*					
	Actual / Latest Forecast					

(8) Revenue from new activities generated by the R&D project and which is accrued to the Singapore office

(9) To provide forecast wherever data are unavailable at point of reporting

Describe how the R&D capabilities have helped your company (as projected by company in the initial project application and replicated in the above table) to:

- increase in market share (to provide a proper definition of the type of market that your company is competing in);
- increase in revenue;
- achieve competitive advantage;
- improve the ranking amongst competitors;
- achieve significant awards, certification, or worldwide recognition;
- etc.

3.5 Other Spin-offs due to R&D Project

Highlight other spin-offs from the R&D Project, such as licensing of technologies developed, establishment of new joint ventures, companies, etc.

3.6 Potential Opportunities

Describe how this Project has created opportunities (as projected in the initial Project application) for your company:

- in terms of new markets or expanded markets;
- potential increase in revenue;
- etc.

4 ***FUTURE PLANS*** **(This section is only relevant for Final Reports)**

Give a brief description of:

- any new significant R&D capabilities that your company plans to develop in the near future.
- any product/process that may be developed in the near future arising from such new R&D capabilities.

---

5 ***DECLARATION***

I declare that the information of the R&D Project as described in the above report is true and to the best of my knowledge.

Signature of Principal Investigator	Date
Signature of CEO	Date

Please retain all the relevant documents in this folder so as to facilitate you in filing and submitting the claims to EDB and for your future reference.

CHECK LIST FOR SUBMISSION OF DOCUMENTS TO EDB

Acceptance Letter

1. Have you signed and returned the acceptance letter to EDB within **1 month** from date of the offer letter?

Interim Claims and Reports

1. Has the Interbank Giro form been completed and submitted together with your 1st claim?
2. Have you submitted the auditor's statement, when due,?
3. Have you submitted the project progress report, when due?
4. Have you used the EDB address labels provided for mailing of the documents to EDB?

Final Claim and Report

1. Is the final claim submitted within **6 months** from the end of the qualifying period?
2. Have you submitted the auditor's statement?
3. Have you submitted the project final report?
4. Have you used the EDB address labels provided for mailing of the documents to EDB?

(std / audit)

Exhibit 10.46

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.R.F §§ 200.80(B)4 AND 240.24B-2

ROBODESIGN INTERNATIONAL

DEVELOPMENT AGREEMENT

This Development Agreement (the "Agreement") is entered into this day of November, 2003 (the "Effective Date"), by and between RoboDesign International, Inc., a Delaware corporation with its principal place of business located at 5920 Pasteur Court, Carlsbad, CA 92008 ("RoboDesign"), and Isis Pharmaceuticals, Inc., a Delaware corporation with its principal place of business located at 2292 Faraday Avenue, Carlsbad, CA 92008, ("Isis").

R E C I T A L S

A. WHEREAS, RoboDesign has developed and is the owner of the copyrights, Patents, trademarks and other intellectual property in certain software and hardware relating to automation motion and vision control, and certain user interfaces to facilitate user intervention with automated devices;

B. WHEREAS, Isis, through its Ibis Therapeutics™ program, is designing a biosensor, called Triangulation Identification Genetic Evaluation of biological Risks ("TIGER") as a tool to rapidly and specifically identify and/or detect infectious agents through their unique genomic sequences; and

C. WHEREAS, Isis desires to engage RoboDesign to develop certain instrumentation and related software to automate the TIGER detection processes.

NOW, THEREFORE, in consideration of the mutual promises and covenants set forth herein, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

A G R E E M E N T

1. Definitions.

1.1 "*Affiliate*" shall mean any person, joint venture, partnership, corporation, trust, unincorporated organization or other entity which, directly or indirectly, controls, is controlled by, or is under common control with another party.

1.2 *"End User"* shall mean the ultimate user of a Tiger 2.0 Instrument in the Field.

1.3 *"Field"* shall mean [***.]

1.4 "*Ibis Software*" means the software developed by Isis (either alone or in collaboration with a third party) for use in the Prototype and/or the Tiger 2.0 Instrument. Ibis software does not include the Work Software.

1.5 "*Isis Technology*" shall mean all Patents, copyrights, copyright applications, trade secrets, trade names, trademarks, formulas, know-how, drawings, sketches, configurations, models, prototypes, machines, designs, software, concepts, schematics, layouts, inventions, processes, and works of authorship owned or controlled by Isis, including without limitation, those related to the biochemical processes used in the TIGER technology and the Ibis Software.

1.6 *"Patent"* shall mean (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; and (d) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part (but only to the extent claiming subject matter previously disclosed in the parent application), re-examinations, renewals and foreign counterparts thereof.

1.7 *"Prototype"* shall mean the initial design and development of a pre-production prototype of the Tiger 2.0 Instrument, which shall include the Work Software and certain RoboDesign Software and may include the Ibis Software. After satisfactory completion of the acceptance tests specified in Sections 2.2, 2.3 and 2.4, the Prototype may be used as a Tiger 2.0 Instrument.

1.8 *"RoboDesign Blocking Technology"* shall mean all Patents, copyrights, copyright applications, trade secrets, trade names, trademarks, formulas, know-how, drawings, sketches, configurations, models, prototypes, machines, designs, software, concepts, schematics, layouts, inventions, processes, and works of authorship owned or controlled by RoboDesign (except for the RoboDesign Software and the RoboDesign Architecture) that are necessary to make, use or sell a Tiger 2.0 Instrument.

1.9 *"RoboDesign Architecture"* shall mean the techniques of using the RoboDesign Software to define a distributed network of individual machine controllers as a system to support a collective process and to schedule, synchronize, configure, control and monitor the individual machines in order to complete specific process jobs, which RoboDesign has developed, or may develop outside of its tasks under this Agreement, and which can be used, among other ways, to assist in the development of the Work Software and the operation of the Tiger 2.0 Instrument.

1.10 *"RoboDesign Software"* shall mean software components including ActiveX controls, class and other library modules, device drivers, and other software objects, relating to automation, motion control, vision systems, image processing, machine control, machine simulation and diagnostics, machine remoting, synchronization and scheduling, machine data collection and visualization, data tracking, recipe and script generation and user interfaces to facilitate user intervention with automated devices, which RoboDesign has developed, or may develop outside of its tasks under this Agreement, and which can be used, among other ways, to assist in the development of the Work Software and the operation of the Tiger 2.0 Instrument. RoboDesign Software does not include the Work Software or the Ibis Software.

1.11 *"Tiger 2.0 Instrument"* shall mean the instrument for the automated detection of infectious agents by use of Isis' TIGER technology, as more fully described in the Specifications attached as *Exhibit B*, or any successor instrument thereto that employs [***.]

1.12 *"Unauthorized Code"* means (i) any software routine designed to disable a computer program automatically or under the positive control of a person other than a licensee of the program and (ii) any software routines or hardware components designed to permit unauthorized access to disable, erase, or otherwise harm software, hardware, or data. Unauthorized Code does not include software routines in a computer program, if any, designed to permit RoboDesign to obtain access to the RoboDesign Software or the Work Software to perform its obligations under this Agreement (e.g., remote access via modem).

1.13 *"Work"* shall mean all work product, services and information, and all intellectual property rights therein, created or developed by RoboDesign under this Agreement, including without limitation, (i) the Prototype, (ii) Patents, copyrights, copyright applications, trade secrets, trade names, trademarks, moral rights, know-how, drawings, sketches, configurations, models, prototypes, machines, designs, computer files containing designs, concepts, schematics, layouts, inventions, processes, ideas, improvements and works of authorship; (iii) the Work Software, including its source code and design documents, (but not the RoboDesign Software) and related enhancements, upgrades, bug fixes and any derivative works thereof; (iv) operator, user and technical manuals relating to such software; and (v) training materials, guides, specifications, listings and any other information concerning the Prototype. "*Work*" shall not include (a) the RoboDesign Architecture and the RoboDesign Software, and (b) the Isis Technology (even if such Isis Technology is integrated with any other Work).

1.14 *"Work Software*" shall mean the software developed by RoboDesign hereunder for use in connection with the Tiger 2.0 Instrument. Work Software does not include the RoboDesign Software or the Ibis Software.

1.15 **Other Definitions.** The following other terms are defined as follows:

"Effective Date" shall have the meaning set forth in the Preamble.

"End User License shall have the meaning set forth in Section 4.3.

"Escrow Agreement" shall have the meaning set forth in Section 4.6(a)

"Factory Acceptance Test" shall have the meaning set forth in Section 2.2.

"Release Event" shall have the meaning set forth in Section 4.6(b)

"Site Acceptance Test" shall have the meaning set forth in Section 2.3.

"Specifications" shall have the meaning set forth in Section 2.1.

"Source Code" shall have the meaning set forth in Section 4.6(a).

2. Product Development.

2.1 **Design & Development of Prototype.** RoboDesign shall use commercially reasonable efforts to design and develop the Prototype, including the Work Software, according to design specifications provided to RoboDesign by Isis and attached as *Exhibit B* (the "Specifications") within [***] months of the Effective Date.

2.2 **Factory Acceptance Test.** Upon completion of the Prototype, RoboDesign shall conduct the testing set forth on *Exhibit C* (the "Factory Acceptance Test"), it being acknowledged that the Factory Acceptance Test shall evaluate [***]. If the Prototype fails to satisfy the Factory Acceptance Test requirements, RoboDesign shall, as soon as practicable, modify the Prototype, at [***] to Isis, and again perform the Factory Acceptance Test as needed until the Prototype successfully meets the Factory Acceptance Test requirements. When the Prototype has successfully satisfied the Factory Acceptance Test, RoboDesign shall give Isis written notice thereof and Isis shall take possession of the Prototype as set forth in Section 2.6 below.

2.3 **Site Acceptance Test.** Promptly upon taking possession of the Prototype, Isis shall conduct the testing set forth on *Exhibit D* (the "Site Acceptance Test"), it being acknowledged that the Site Acceptance Test shall evaluate [***]. If the Prototype fails to satisfy the Site Acceptance Test requirements, RoboDesign shall, as soon as practicable, modify the Prototype, at [***] to Isis, and Isis shall again perform the Site Acceptance Test as needed until the Prototype successfully meets the Site Acceptance Test Requirements. When the Prototype has successfully satisfied the Site Acceptance Test, Isis shall give RoboDesign written notice thereof.

2.4 **Biochemical Acceptance Test.** Promptly upon taking possession of the Prototype, Isis shall conduct the testing set forth on *Exhibit E* (the "Biochemical Acceptance Test"). If the Prototype fails to satisfy the Biochemical Acceptance Test requirements, RoboDesign shall, as soon as practicable, modify the Prototype (i) at [***] to Isis if the failure to satisfy the Biochemical Acceptance Test is due to the Prototype's failure to meet the Specifications (as updated by mutually agreed change requests under Section 2.7 through the time of such failure) or (ii) at [***] to the extent such modification requires new change requests under Section 2.7 to correct the failure to satisfy the Biochemical Acceptance Test, and Isis shall again perform the Biochemical Acceptance Test as needed until the Prototype successfully meets the Biochemical Acceptance Test Requirements. When the Prototype has successfully satisfied the Biochemical Acceptance Test, Isis shall give RoboDesign written notice thereof.

2.5 **Development Fee Payments.** Isis agrees to pay to RoboDesign all development fees as set forth on *Exhibit F* (the "Development Fees") within [***] days of the applicable due date specified on *Exhibit F* by wire transfer to a bank account designated by RoboDesign or by check payable to RoboDesign. In the event any payment of the Development Fees are not made when due such unpaid Development Fees shall bear interest at the rate of [***]% per month, or the maximum rate as permissible by law, whichever is less. All Development Fees shall be non-refundable.

2.6 **Delivery.** Following satisfactory completion of Factory Acceptance Testing, RoboDesign shall deliver the Prototype to Isis at RoboDesign's facilities in Carlsbad, California. Title and risk of loss shall pass to Isis when Isis takes possession of the Prototype at RoboDesign's facilities. In addition to the Prototype, RoboDesign will deliver to Isis the Work.

2.7 **Change Requests.** In the event Isis requests modifications to the design specifications for the Prototype which are beyond the scope of the original design specifications, RoboDesign agrees to cooperate with Isis to accommodate reasonable changes to such design specifications; *provided*, *however*, that if any such changes or alternative or additional design specifications require RoboDesign to invest additional resources (including personnel resources) beyond what is contemplated by the then-current design specifications, or will result in additional costs to RoboDesign, then RoboDesign will provide a quote for such changes and if Isis agrees, RoboDesign will undertake the changes and Isis shall pay per the quote in accordance with the terms defined in Exhibit F. If any Isis change request will impact a delivery schedule previously agreed upon by the parties, RoboDesign shall notify Isis and the parties shall make reasonable and appropriate adjustments to such delivery schedule.

3. Ownership of Technology.

Subject to the rights set forth in Section 4 below:

3.1 **Work for Hire.** RoboDesign hereby agrees that all Work has been specially ordered and commissioned by Isis and shall be "works made for hire" for copyright purposes. Isis shall exclusively own all Work, including, without limitation, all Patent, trade secret and copyright rights therein.

3.2 **Assignment.** RoboDesign hereby assigns to Isis, its successors and assigns, all rights, title and interest in and to the Work including, without limitation, the following:

(a) any U.S. copyrights that RoboDesign may possess or acquire in the Work and all copyrights and equivalent rights in the Work throughout the world, including all renewals and extensions of such rights that may be secured under the laws now or hereafter in force and effect in the United States of America or in any other country or countries;

(b) all rights in and to any inventions, ideas, designs, concepts, techniques, discoveries, or improvements, whether or not patentable, embodied in the Work or developed in the course of RoboDesign's creation of the Work, including, but not limited to, all trade secrets, utility and design Patent rights and equivalent rights in and to such inventions and designs throughout the world, regardless of whether or not legal protection for the Work is sought;

(c) any documents, drawings, magnetically or optically encoded media, or other materials created by RoboDesign under this Agreement; and

(d) the right to sue for infringements, which may occur before the date of this Agreement, and to collect and retain damages from any such infringements.

3.3 **Further Assistance.** At Isis' expense, RoboDesign shall take all actions and execute and deliver all documents as Isis may reasonably request to effectuate the acknowledgement of ownership herein and vesting of complete and exclusive ownership of the Work in Isis. RoboDesign will provide reasonable assistance to Isis and its attorneys and agents in securing any of the patent or other proprietary rights provided for in this Section 3.3, including to effectuate the acknowledgement of

ownership contained herein and the vesting of complete and exclusive ownership of the Work in Isis, and to secure, maintain and defend for Isis' own benefit all rights therein, including the right to submit any Patent, copyright or trademark application or registration.

3.4 **Isis Technology.** RoboDesign shall have no right, title or interest in or to the Isis Technology.

4. Licenses.

4.1 **Grant-Back of License in the Work by Isis.** Isis hereby grants to RoboDesign an irrevocable, perpetual, worldwide, royalty-free, non-exclusive, transferable and assignable license, with the right to sublicense, solely to use, modify, copy, incorporate, create derivative works from, manufacture and have manufactured products incorporating the Work for applications outside the Field.

4.2 **Grant of License in the Isis Technology by Isis.** During the term of this Agreement, Isis hereby grants to RoboDesign a, nonexclusive, nonassignable, nontransferable royalty-free license to use, modify, copy, incorporate, create derivative works from the Isis Technology solely for the purpose of performing RoboDesign's obligations under this Agreement.

4.3 **Software License by RoboDesign.** RoboDesign hereby grants to Isis (i) a non-exclusive, limited license to deliver one (1) copy of the RoboDesign Software (in binary executable form) together with a Tiger 2.0 Instrument to an End User, (ii) a limited right to grant a sublicense to each End User to use one (1) copy of the RoboDesign Software in conjunction with each Tiger 2.0 Instrument only, provided that such sublicense is granted pursuant to an end user license agreement (the "End User License Agreement") with terms no less protective of RoboDesign's rights than those set forth on *Exhibit G* hereto. The license rights granted under clauses (i) and (ii) of this Section 4.3 are sublicensable, transferrable and/or assignable only to (x) the United States government, (y) a partner of Isis that has agreed to make or commercialize a Tiger 2.0 Instrument, or (z) as permitted under Section 10.9.

4.4 **Unblocking License by RoboDesign.** RoboDesign hereby grants to Isis a non-exclusive, license to practice the RoboDesign Blocking Technology and the RoboDesign Architecture solely to the extent necessary to make, use or sell a Tiger 2.0 Instrument in the Field. This license is sublicensable to End Users and the United States government, and is assignable to a partner of Isis that has agreed to make or commercialize a Tiger 2.0 Instrument or as permitted under Section 10.9.

4.5 **Government Rights.** The licenses granted under this Section 4.1and 4.2 are subject to the rights of the United States Government as set forth in 35 U.S.C. § 200 *et seq*. If there is any conflict between such rights and the rights granted herein, such government rights will prevail.

4.6 **Source Code Escrow.**

(a) **Escrow Agreement.** If requested by Isis in writing, within 30 days of such request RoboDesign will deliver one (1) copy of the RoboDesign Software incorporated in the Tiger 2.0 Instrument in source code form (the "Source Code") along with documentation as to the applicable use of the RoboDesign Architecture, to an escrow agent to be mutually determined by the parties (the "Escrow Agent"), and at such time, RoboDesign, Isis and the Escrow Agent shall enter into the Escrow Agreement (the "Escrow Agreement"), which shall, among other things, reflect the terms set forth in this Section 4.6. All fees and expenses charged by the Escrow Agent will be borne by Isis.

(b) **Release Events for Source Code**. The Source Code and related documentation shall be released from escrow and delivered to Isis upon the occurrence of one or more of the following events (each, a "Release Event"): (I) if RoboDesign becomes insolvent or admits insolvency or admits a general inability to pay its debts as they become due; (II) if RoboDesign files a petition

for protection under the Bankruptcy Code of the United States, or an involuntary petition in bankruptcy is filed against RoboDesign and is not dismissed within sixty (60) days thereafter; (III) if RoboDesign or its successor with respect to this Agreement ceases operations as a going concern or (IV) RoboDesign refuses to or is unable to honor the warranty set forth in Section 5.1 or provide post warranty service under Section 5.2.

(c) **Effect of Release Event**. Upon the occurrence of a Release Event and the delivery of the Source Code and related documentation to Isis, Isis shall have right only to use the Source Code and related documentation to maintain and upgrade the software in the Tiger 2.0 Instrument (including those being used by End Users) in accordance with the scope of the License set forth in Section 4.3 and shall have no right to use the RoboDesign Software, the Source Code or related documentation to design, develop, use or market any other products. All right, title and interest in and to the Source Code and all related documentation, and all copyrights, Patents, trademarks, service marks or other intellectual property or proprietary rights related thereto are and shall remain solely with RoboDesign, both prior to and after the occurrence of the Release Event. Isis acknowledges that no other right, title or interest in or to the Source Code or related documentation is granted under this Agreement, and that no such assertion shall be made by Isis either prior to or after the occurrence of the Release Event. Isis shall treat the Source Code and the related documentation as Proprietary Information pursuant to Article 7 below.

5. Warranties, Indemnity, Limitations of Liability, Insurance

5.1 **Limited Warranty, Warranty Service.**

(a) RoboDesign expressly warrants to Isis that the Prototype shall conform with the Specifications and be free from defects in materials and workmanship for a period of [***] months following the date the Prototype satisfactorily completes the Site Acceptance Test (the "Warranty Period"), it being acknowledged that such warranty covers only the electromechanical operation of the Prototype and not the efficacy of the biochemical tests performed by the Prototype. The terms of *Exhibit H* shall apply to RoboDesign's warranty hereunder. RoboDesign's liability under this warranty shall be limited, at its option, to replacing or repairing Prototype shown to be defective in materials or workmanship. A claim of defective materials or workmanship in the Prototype shall be allowed only when it is submitted to RoboDesign in writing within [***] days after discovery by Isis or the End User of the defect, and in any event, within the Warranty Period.

(b) To the best of its knowledge, RoboDesign represents and warrants to Isis that the RoboDesign Software and the Work Software provided to Isis by RoboDesign under this Agreement does not contain or will not contain any Unauthorized Code. If RoboDesign discovers (whether on its own or through notice) any Unauthorized Code in the RoboDesign Software or Work Software provided to Isis under this Agreement, RoboDesign will promptly remove such Unauthorized Code.

5.2 **Post Warranty Period Service.** At Isis' option, RoboDesign shall provide service on the Prototype after the Warranty Period on terms set forth on *Exhibit H*.

5.3 **Assignment of Warranties.** If material incorporated in the Prototype contains one or more manufacturer's or supplier's warranties, RoboDesign hereby assigns such warranties to Isis to the extent such warranties are assignable. RoboDesign will use commercially reasonable efforts to secure the ability to assign such warranties to Isis. RoboDesign will cooperate with Isis to enable Isis to benefit from any such warranties that are not assignable. Upon Isis' request, RoboDesign will provide to Isis a copy of such warranties. Isis may transfer or assign the warranty under Section 5.1 to an End User.

5.4 **Intellectual Property Warranty.** RoboDesign represents and warrants that to its knowledge none of the devices and methods included in the Prototype, when delivered to Isis under Section 2.6, will infringe any intellectual property rights in the United States of any third party.

5.5 **No Other Warranties.** EXCEPT FOR THE EXPRESS WARRANTIES CONTAINED HEREIN, ROBODESIGN MAKES NO WARRANTY HEREUNDER OF ANY KIND WHATSOEVER, EXPRESS OR IMPLIED, AND ALL WARRANTIES OF MERCHANTABILITY, NONINFRINGEMENT AND FITNESS FOR A PARTICULAR PURPOSE ARE HEREBY DISCLAIMED BY ROBODESIGN.

5.6 **Indemnity by Isis.** Isis shall indemnify and hold RoboDesign harmless from and against any liability, losses, damages, claims, costs and expenses (including reasonable fees of attorneys and other professionals and court costs) arising from any claim, action or cause of action related to the use, manufacture, marketing or sale of Tiger 2.0 Instruments (including the Prototype), unless such claim relates to (i) infringement of third party intellectual property which was known to RoboDesign prior to, or during its conduct of the Work or (ii) infringement of third party intellectual property through the use of the RoboDesign Software as permitted under this Agreement. Subject to the terms and conditions of this Agreement, Isis shall have the primary responsibility for defending against any such claims, whether arising under theories of negligence, strict liability, tort, product liability of otherwise.

5.7 **Indemnity by RoboDesign.** RoboDesign shall indemnify and hold Isis harmless from and against any liability, losses, damages, claims, costs and expenses (including reasonable fees of attorneys and other professionals and court costs) arising from (A) RoboDesign's breach of Section 5.1(b), or (B) a claim, action or cause of action alleging that (i) the use of Tiger 2.0 Instruments (in the form of the Prototype that has successfully completed the Site Acceptance Test), infringes a third party's intellectual property which was known to RoboDesign prior to, or during its conduct of the Work, or (ii) the use of RoboDesign Software

as permitted under this Agreement, infringes a third party's intellectual property; *provided, however*, that RoboDesign will have no liability under this clause (ii) for any alleged infringement to the extent arising from (y) any modification of the RoboDesign Software by Isis or an End User or (z) the use of the RoboDesign Software in combination with technology provided by Isis. Subject to the terms and conditions of this Agreement, RoboDesign shall have the primary responsibility for defending against any such claims.

5.8 **Indemnity Procedures.** Each Party's agreement to indemnify and hold the other harmless is conditioned upon the indemnified Party (i) providing written notice to the indemnifying Party of any claim, demand or action arising out of the indemnified activities within [***] days after the indemnified Party has knowledge of such claim, demand or action, (ii) permitting the indemnifying Party to assume full responsibility to investigate, prepare for and defend against any such claim or demand, (iii) assisting the indemnifying Party, at the indemnifying Party's reasonable expense, in the investigation of, preparation of and defense of any such claim or demand; and (iv) not compromising or settling such claim or demand without the indemnifying Party's prior written consent.

5.9 **Limitation of Liability.** IN NO EVENT SHALL EITHER PARTY BE LIABLE TO THE OTHER FOR LOSS OF PROFITS OR SPECIAL, INCIDENTAL OR CONSEQUENTIAL DAMAGES REGARDLESS OF WHETHER SUCH PARTY WAS ADVISED, HAD OTHER REASON TO KNOW OR IN FACT KNEW OF THE POSSIBILITY.

5.10 **Insurance.** For so long as any Tiger 2.0 products are in use and for [***] years following the discontinuation of such use, Isis shall at its own cost and expense, obtain and maintain in full force and effect, commercial, general liability insurance, including personal injury and products liability coverage or require its commercialization partners to obtain and maintain such insurance. If required, Isis will provide RoboDesign with a certificate of insurance evidencing the above and showing the name of the issuing company, the policy number, the effective date, the expiration date and the limits of liability. Isis will provide RoboDesign with written notice before Isis cancels such insurance.

6. Term; Termination.

6.1 **Term of Agreement.** The term of this Agreement shall commence on the date hereof and continue until successful completion of the Site Acceptance Test, unless canceled or terminated earlier in accordance with the provisions of this Agreement.

6.2 **Default Termination.** In the event of a material default under this Agreement by either party, which breach is not cured within [***] days (or [***] days in the event of a payment default) after the defaulting party's receipt of written notice thereof, the nondefaulting party shall be entitled to terminate this Agreement, effective at the end of such cure period; *provided, however* that, once a Prototype has been delivered under Section 2.6, RoboDesign may not terminate the licenses granted under Sections 4.3 and 4.4 for a material breach (except for a breach of Section 2.5) to the extent such licenses are necessary to make, use and sell a Tiger 2.0 Instrument. Notwithstanding anything to the contrary stated hereinabove, in addition to and in lieu of its rights to terminate this Agreement upon a material breach by either party, the other party shall have the right to pursue any remedies available to it at law or in equity.

6.3 **Termination for Failure.** If (A) RoboDesign fails to deliver to Isis a Prototype that meets the material requirements of the Specifications after (i) the delivery schedule set forth in Section 2.1 lapses (as may be extended from time to time pursuant to Section 2.7) and (ii) [***] days from the date Isis provides RoboDesign with a reasonably detailed written notice of why the Prototype does not meet the material requirements of the Specifications, (B) and such failure results because RoboDesign did not use commercially reasonable efforts to satisfy its obligations under this Agreement, then Isis may, at its option, terminate this Agreement by providing RoboDesign with written notice thereof and returning to RoboDesign all Work and equipment purchased by RoboDesign and provided to Isis hereunder. In such event, (i) Robodesign will return to Isis (i) all equipment and materials provided by Isis to RoboDesign hereunder and all payments made to Robodesign under this Agreement and (ii) any accrued payment obligations under this Agreement will terminate and not survive within 60 days of such termination.

6.4 **Insolvency Termination.** In the event either party shall go into liquidation, or have a receiver or trustee appointed for its property or estate, or shall make an assignment for the benefit of creditors, whether any of the aforesaid events be the outcome of a voluntary act or otherwise, the other party shall be entitled by notice to terminate this Agreement forthwith.

6.5 **Termination by Isis for Convenience.** Isis may terminate this Agreement at any time upon thirty (30) days notice to RoboDesign. In such event Isis will pay RoboDesign for the services it provided through the date of such termination on a time and materials basis at the rates set forth on Exhibit F hereto and RoboDesign will refund to Isis the amount of any funds already paid to RoboDesign that may exceed the amount owing for the time and materials.

6.6 **Continuing Obligations.** Sections 3, 4.1, 4.5, 4.6, 5, 6, 7, 8, 9 and 10 shall survive the termination or expiration of this Agreement. Sections 4.3 and 4.4 shall survive the expiration or termination of this Agreement only if pursuant to Section 6.1, Section 6.2 because of material breach by RoboDesign, Section 6.4 because of insolvency of RoboDesign, or as specified in Section 6.2. Any sublicense or assignment of warranty granted by Isis to an End User under Section 4.3 will survive termination of this Agreement.

7. Confidential Information.

7.1 Both RoboDesign and Isis have made and will continue throughout the term of this Agreement to make available to the other party its confidential and proprietary materials and information ("Proprietary Information"). All material and information provided by one party to the other party relating to the business, policies, procedures, customs and forms of providing party or any

of its Affiliates (including, without limitation, the RoboDesign Technology, the Isis Technology, and the Prototype) as well as information previously divulged or delivered regarding the aforementioned subject matter, is hereby designated as confidential and proprietary and shall be considered to be Proprietary Information of the disclosing party. It is understood that the obligations set forth above in this Section 7.1 do not apply to materials or information that: (a) are already, or otherwise become, generally known by third parties, except as a result of a wrongful act or omission of the receiving party; (b) are generally furnished to others by the disclosing party without restriction on disclosure; (c) were already known by the receiving party prior to receiving them from the disclosing party and were not received from a third party in breach of that third party's obligations of confidentiality; or (d) are independently developed by the receiving party without the use of Proprietary Information of the disclosing party.

7.2 The receiving party shall maintain the confidentiality of the disclosing party's Proprietary Information, will not disclose such Proprietary Information without the prior written consent of the disclosing party, and will use such Proprietary Information solely to perform its obligations hereunder. Each party shall also keep confidential the terms of this Agreement and/or any Exhibit hereto, except that either party may disclose such terms to its legal, accounting or financial advisors.

7.3 Neither party's obligations of confidentiality will prevent or prohibit the parties from providing access to Proprietary Information upon request of a state or federal regulatory agency or authority as may be required by law or judicial or administrative process. Notwithstanding the foregoing, in the event of any requested access to Proprietary Information by a regulatory authority, the party from whom the Proprietary Information is requested will provide written notice to the other party in a timely fashion to allow the other party the opportunity to contest the release of its Proprietary Information to such regulatory authority.

7.4 RoboDesign will not disclose the terms or existence of this Agreement without the prior written consent of Isis unless such disclosure is made pursuant to a confidential disclosure agreement with terms substantially similar to those contained in Sections 7.1 through 7.3.

8. Noncompetition. During the term of this Agreement and for [***]years thereafter, RoboDesign will not develop or commercialize, or assist in the development or commercialization of [***].

9. Export Compliance. Unless an appropriate license, exemption, or similar authorization has been duly obtained, Isis shall not, nor shall Isis authorize its employees, distributors, customers, and/or agents to, export or re-export the Prototype or a Tiger 2.0 Instrument (including any information relating thereto) to any country specified as a prohibited destination in applicable U.S. laws, regulations, and ordinances, including the Regulations of the U.S. Department of Commerce and/or other government agencies. Isis agrees to defend, indemnify, and hold harmless RoboDesign from and against any claim, loss, liability, expense, or damage (including liens or legal fees) incurred by RoboDesign with respect to any of Isis' export or re-export activities contrary to the foregoing instructions (subject to the procedures set forth in Section 5.8).

10. Miscellaneous.

10.1 **ISO 9001.** RoboDesign represents and warrants that it will maintain at its sole expense its ISO 9001 or ISO 9002 certifications and will apply an ISO 9001 and/or ISO 9002 (as applicable) compliant quality system to the design and manufacture of the Prototype.

10.2 **Force Majeure.** Neither party shall be liable for failures or delays (not to exceed [***] months) in performance hereunder due to fire, explosion, breakdown of plant, lockout, casualty or accident, acts of God or the public enemy, interference by civil or military authority, compliance with

applicable laws of the United States of America or of any other governmental authority, or any other similar cause beyond the control of the party in question.

10.3 **Construction; Interpretation.** The headings contained in this Agreement are for reference purposes only and shall not affect in any way the meaning or interpretation of this Agreement. Any article, section, recital, exhibit, schedule and party references are to this Agreement unless otherwise stated. No party, nor its counsel, shall be deemed the drafter of this Agreement for purposes of construing the provisions of this Agreement, and all provisions of this Agreement shall be construed in accordance with their fair meaning, and not strictly for or against any party.

10.4 **Notices.** Any notice, demand, approval, consent, or other communication required or desired to be given under this Agreement shall be in writing and shall be (i) personally served, (ii) mailed in the United States mail, certified, return receipt requested, postage prepaid, or (iii) sent via commercial overnight courier, in each case addressed to the party to be served with the copies indicated below, at the last address given by that party to the other under the provisions of this section. All such communications shall be deemed delivered at the earlier of actual receipt or (i) three (3) business days following mailing by U.S. mail or (ii) one (1) business day following deposit with a commercial overnight courier.

RoboDesign:	RoboDesign International, Inc. 5920 Pasteur Court Carlsbad, CA 92008 Attn: Chief Executive Officer
With a copy to:	Stradling Yocca Carlson & Rauth 660 Newport Center Drive, Suite 1600 Newport Beach, California 92660 Attn: Lawrence B. Cohn
Isis:	Isis Pharmaceuticals, Inc. 2292 Faraday Avenue Carlsbad CA 92008 Attn: David J. Ecker, Ph.D.
With a copy to:	Isis Pharmaceuticals, Inc. 2292 Faraday Avenue Carlsbad CA 92008 Attn: General Counsel

10.5 **Further Assurances.** Each party agrees to cooperate fully with the other and execute such instruments, documents and agreements and take such further actions to carry out the intents and purposes of this Agreement.

10.6 **Severability.** If any term, provision, covenant or condition of this Agreement is found by a court of competent jurisdiction to be invalid, void or unenforceable, then such term, provision, covenant or condition shall be deemed to be stricken from this Agreement and the remainder of this Agreement shall remain in full force and effect and shall in no way be effected, impaired or invalidated thereby.

10.7 **Governing Law; Arbitration.** This Agreement shall be governed by, and construed in accordance with the laws of the State of California, without reference to rules of conflict or choice of laws that could result in the application of laws of another jurisdiction. All disputes, differences or questions arising out of this Agreement or as to the rights or obligations of the parties hereunder or in connection herewith or as to the construction or interpretation hereof shall be attempted to be resolved

by discussion between the CEO of RoboDesign and the Executive Vice President of Isis. Any such disputes which cannot be so resolved within thirty (30) days of written notification to the CEO of RoboDesign and the CEO of Isis detailing the nature of the dispute(s) shall be referred to binding arbitration, held in San Diego, California, before a single arbitrator in accordance with the Commercial Arbitration Rules of the American Arbitration Association.

10.8 **Independent Contractor Status, No Agency.** RoboDesign's and Isis' activities hereunder shall be conducted as independent contractors and no agency relationship shall exist between the parties. Neither party shall represent to any third party that it is an agent or Affiliate of the other party.

10.9 **Assignment.** This Agreement shall not be assignable by either party without the consent of the other party, which shall not be unreasonably withheld. Notwithstanding the foregoing, either party may, without the other's consent, assign or otherwise transfer this Agreement or any right or obligation hereunder to any affiliate or in connection with the transfer or sale of the business (whether by merger, sale of stock or sale of assets) to which this Agreement relates. All the terms, covenants and conditions of this Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns.

10.10 **Parties in Interest.** Nothing in this Agreement, whether express or implied, is intended to confer any rights or remedies under or by reason of this Agreement on any persons other than the parties to it and their respective successors, permitted sublicensees and assigns, nor is anything in this Agreement intended to relieve or discharge the obligation or liability of any third persons to any party to this Agreement, nor shall any provision give any third persons any right of subrogation or action over or against any party to this Agreement.

10.11 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which shall be deemed an original and all of which, taken together, shall constitute one instrument.

10.12 **Entire Agreement; Amendment.** This Agreement (including all Exhibits hereto) sets forth the entire understanding and agreement between the parties with respect to the subject matter hereof, and supersedes and replaces any prior understanding, agreement or statement, written or oral, with respect to the same. Any terms of any purchase order, confirmation or invoice, whether or not signed, are expressly rejected and shall be superseded by this Agreement. The parties hereto expressly agree and confirm that this Agreement is executed without reliance on any oral or written statements, representations or promises of any kind which are not expressly contained in this Agreement. This Agreement, and the Exhibits hereto, shall not be modified except by a writing signed on behalf of each of the parties hereto.

IN WITNESS WHEREOF, the parties have executed this Development Agreement as of the Effective Date.

"RoboDesign"

ROBODESIGN INTERNATIONAL, INC.,
a Delaware corporation

By: /s/ ROBERT COREY

Its: CEO

"Isis"

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: /s/ B. LYNNE PARSHALL

Its: EVP and CFO

EXHIBIT B

SPECIFICATIONS

[***]

Specifications include Developer Kit to allow Isis to modify system protocols, control logic and parameters independently of RoboDesign

EXHIBIT C

FACTORY ACCEPTANCE TEST

The specifics of the Factory Acceptance Test will be agreed upon by the Parties within 30 days of the Effective Date

---

EXHIBIT D

SITE ACCEPTANCE TEST

The specifics of the Site Acceptance Test will be agreed upon by the Parties within 30 days of the Effective Date

---

EXHIBIT E

BIOCHEMICAL ACCEPTANCE TEST

The specifics of the Biochemical Acceptance Test will be agreed upon by the Parties within 30 days of the Effective Date

---

EXHIBIT F

DEVELOPMENT FEES

Development Fees

[***]

Payment Schedule

[***]payable on Effective Date

[***] payable [***] days from Effective Date

[***] payable on successful completion of Factory Acceptance Test

[***] payable on successful completion of Site Acceptance Test, provided, however that if Isis fails to complete the Site Acceptance Test within [***] days following successful completion of the Factory Acceptance Test, the aforementioned [***] shall be due and payable by Isis at the end of such [***] days.

[***] payable on successful completion of Biochemical Acceptance Test, provided, however that if Isis fails to complete the Biochemical Acceptance Test within [***] days following its payment of the [***] set forth above, the remaining [***] shall be due and payable by Isis at the end of such [***] days.

Design Changes:

RoboDesign may at its (i) option bill [***] of the incremental cost attributable to such design change upon acceptance of change order by Isis and [***] upon completion and acceptance of such design change, due upon receipt of invoice; or (ii) Bill for Isis approved changes upon completion, due upon receipt of invoice.

Purchase Price of Developer Kit (as described in the Specifications): [***]

TIME & MATERIALS PRICING

Senior Management—[***] per hour

Project Management—[***] per hour

Software Engineer—[***] per hour

Mechanical & Electrical Engineer—[***] per hour

Field Service Technicians—[***]

All other employees—[***] per hour

Materials—Priced at a Prime Profit rate of [***].

EXHIBIT G

MINIMUM END USER LICENSE

Important—read carefully: this document is a legal agreement between you, the Licensee, and Isis Pharmaceuticals, the Licensor, for this software product. By installing or otherwise using the software product, you agree to be bound by the terms of this agreement.

1. GRANT OF LICENSE. In consideration of payment of the license fee, which is part of the price paid for this product, Licensor grants to the Licensee a non-exclusive, non-transferable license, without right to sublicense, to use this copy of the enclosed software on the single computer in conjunction with the equipment on which it was provided at a single location. Licensor reserves all rights not expressly granted to Licensee.

2. OWNERSHIP OF SOFTWARE. As between Licensee and Licensor, title to, ownership of, and all rights and interests in, the software and software documentation, and all copies thereof remains at all times vested in Licensor. The license granted by this Agreement and your payment of the license fee gives you the right to use the software in accordance with the terms of this Agreement. This license is not a sale of the original software or any copy.

3. COPY RESTRICTIONS. This software and the accompanying written materials are copyrighted. Unauthorized copying of the software, including software that has been modified, merged, or included with other software, or other written materials is expressly forbidden. You may be held legally responsible for any copyright infringement that is caused or incurred by your failure to abide by the terms of this license. Subject to these restrictions, you may make one (1) archival copy of the software solely for backup purposes as permitted by 17 U.S.C. § 117. You must reproduce and include the original copyright notice with the copy. This clause does not provide any rights beyond those provided by 17 U.S.C. § 117.

4. USE RESTRICTIONS. As the Licensee, you may not electronically transfer the software from one computer to another over a network. You may not disclose, publish, translate, release, or distribute copies of the software or accompanying written materials to others. You may not modify, adapt, translate, or create derivative works based on the written materials without the prior written consent of Licensor. You may not loan, rent, lease, sell or transfer the software to another user except as part of the permanent transfer of all software, written materials and hardware with which the software was delivered.

5. TERMINATION. This license is effective until terminated. This license will terminate automatically without notice if you fail to comply with any provision of this license. Upon termination you shall destroy the written materials and all copies of the software, including modified copies, if any.

6. LIMITED WARRANTY. Licensor warrants to the original media on which the software is (are) recorded is (are) free from defects and materials and workmanship under normal use and service for a period of ninety (90) days from the date of delivery as evidenced by a copy of the sales receipt. Further, Licensor hereby limits the duration of any implied warranty(ies) on the media to the period stated above. Some states do not allow limitations on duration of an implied warranty, so the above limitation may not apply to you.

7. DISCLAIMER OF WARRANTY AND LIMITED WARRANTY. The software and accompanying written materials, including instructions for use, are provided "as is" without warranty of any kind, either express or implied. Further, Licensor does not warrant, guarantee, or make any representations regarding the use, or the results of the use, of the software or written materials in terms of accuracy, reliability, currentness, or otherwise. The entire risk as to the results and performance of the software is assumed by you. If the software or written materials are defective, the Licensor or its dealers, distributors, agents, or employees, are not responsible for the cost of any

necessary servicing, repair, or correction. Licensor's entire liability and your exclusive remedy as to the media will be, at Licensor's option, either (a) return of the purchase price or (b) replacement of the media that does not meet limited warranty and which is returned to Licensor with a copy of the sales receipt. If failure of the media has resulted from accident, abuse, or misapplication, Licensor shall have no responsibility to replace the disk or refund the purchase price. Any replacement media is warranted for the remainder of the original warranty period or thirty (30) days, whichever is longer.

Except as stated above the software provided and the documentation are provided without warranties of any kind, either express or implied, including but not limited to the implied warranties of non-infringement, merchantability and fitness for a particular purpose. No oral or written information or advice given Licensor its dealers, distributors, agents, or employees shall create a warranty or in any way increase the scope of this warrant, and you may not rely on any such information or advice. This warranty gives you specific legal rights. You may have other rights, which vary from state to state.

Neither Licensor nor anyone else who has been involved in the creation, production, or delivery of this product shall be liable for any direct, indirect, consequential, or incidental damages, including damages for loss of business profits, business interruption, loss of business information, and the like (arising out of the use of or inability to use such products) even if Licensor has been advised of the possibility of such damages. Because some states do not allow the exclusion or limitation of liability for consequential or incidental damages, the above limitation may not apply to you.

8. MISCELLANEOUS. This Agreement expresses the entire agreement between Licensor and the LICENSEE and supersedes any prior communications, oral or written relating to this software. This Agreement is governed by the laws of the State of California

9. U.S. GOVERNMENT RESTRICTED RIGHTS. The software and documentation is provided with RESTRICTED RIGHTS. Use, duplication, or disclosure by the Government is subject to restrictions as set forth in subparagraph (c)(1)(ii) of the Rights in Technical Data and Computer Software clause at DFARS 252.227-7013. Contractor/manufacturer is , located at . Should you have any questions concerning this Agreement, or if you desire to contact Licensor, please write to: , located at .

EXHIBIT H

STANDARD WARRANTY TERMS

RoboDesign provides a limited warranty as standard with all of its products. During the coverage term, technical support as well as software upgrades are provided free of charge. This will allow our service engineers to quickly address any initial problems thus ensuring accurate and reliable system performance.

Warranty Features

- ***Coverage Terms***
  [***] month for parts and labor. Unlimited technical support via phone or email. 1-2 business hour response and on-site support while the prototype system is located in the San Diego area.

- ***Software***
  All software updates and upgrades, as released during the term. Includes updated manuals and other support documentation.

- ***On-site Emergency Visits***

  Unlimited as needed.

Summary of Services	
Period of Service Coverage	Monday-Saturday, 8am-5pm excluding holidays, or as needed for emergency visits
Parts	Included for [***] months
Labor	Included for [***] months
Telephone and Email Response	1-2 business hours
Emergency Visits	As needed
Emergency Visit Response	Same day while prototype system is located in San Diego, 2-3 business day if elsewhere
Preventative Maintenance Visits	As needed
Travel Expenses	Included
Software Revisions and Upgrades	Included
Training	As needed

Exhibit 14

CODE OF ETHICS AND BUSINESS CONDUCT

March 3, 2004

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

TABLE OF CONTENTS

ISIS
CODE OF ETHICS AND BUSINESS CONDUCT

I. PHILOSOPHY OF ISIS CODE OF ETHICS AND BUSINESS CONDUCT

Isis Pharmaceuticals, Inc. (hereinafter referred to as "Isis" or the "Company") will adhere to high legal and ethical standards. As such, this Code of Ethics and Business Conduct (hereinafter referred to as the "Code of Ethics") applies to each of Isis' employees (including its executive officers) and each member of the Isis Board of Directors.

II. COMPLIANCE WITH LAWS AND REGULATIONS

As a U.S. company, Isis is governed by and required to comply with U.S. federal law. In addition to complying with federal law, Isis will conduct all its activities in compliance with all applicable national, state and local laws, regulations and judicial decrees wherever it conducts business.

At no time will you take any action on behalf of the Company that you know, or reasonably should know, violates any law or regulation. Whenever possible, you will strive to comply with the spirit of the law as well as its letter.

No code of conduct can cover all circumstances or anticipate every situation. When you encounter situations not addressed specifically by this Code of Ethics, you should apply its overall philosophy and concepts to the situation. You should also refer to specific Company policies on the subject in question or similar subjects. If you still have a question about the appropriateness of an action, you should review the particular circumstances with Isis' Executive Vice President, CEO or the Audit Committee of the Board of Directors.

III. ETHICAL CONDUCT

You should strive to act in a manner using good judgment, high ethical standards and honesty in your business dealings on behalf of the Company. Unethical practices and activities do not serve the interests of the Company or the community, even if they do not technically violate the law.

A. *Your Responsibilities*

1. Know and comply with the Isis Code of Ethics and Company policies that apply to business activities.

2. Be honest, fair and trustworthy in all business activities and relationships.

3. Provide and support a culture that values integrity and ethical conduct.

4. Avoid all conflicts of interest between work and personal affairs.

5. Report suspected violations of law, the Isis Code of Ethics or Company Policies.

6. Cooperate in any investigation into possible violations of law, the Isis Code of Ethics or Company Policies.

B. *Business Practices*

It is Isis' policy to deal with its business associates, partners, suppliers, competitors and any governments or governmental agencies with which it interacts in an ethical manner. As such, you will comply with the principles outlined below and will take steps to ensure similar compliance by the persons you directly manage.

1. Interaction with Competitors

As a vigorous competitor in the marketplace, Isis will seek economic knowledge about our competitors. However, you will not engage in illegal or improper acts to acquire any competitor information. In addition, you will not hire competitors' employees for the purpose of obtaining confidential information, urge competitors' personnel, customers or suppliers to disclose confidential information, or seek such information from competitors' employees subsequently hired by the Company.

2. Bribes, Kickbacks & Similar Payments

You are prohibited from paying or receiving any bribe, kickback or other similar payment to or from any public official, or government, or other individual, to secure any concession, contract or other favorable treatment for Isis or you. This prohibition extends to the payment or receipt of money or anything else of substantial value when you have reason to believe that some part of the payment or "fee" will be used for a bribe, kickback or other similar activity.

Because Isis is a global company and does business worldwide, you must comply with the United States Foreign Corrupt Practices Act of 1977. For more detail, read a definition of the "Foreign Corrupt Practices Act," attached as Appendix A.

3. Books, Records & Information Management

Isis' books of account and records must be accurately maintained and fully disclose the nature of transactions reflected in them. Penalties for violating the laws and regulations in this area could be severe for the Company and the employees involved. Isis will maintain these books according to the following record-keeping requirements and in compliance with the spirit and letter of applicable laws and regulations:

- All books, records and accounts must be kept in reasonable detail and must accurately and fairly reflect all transactions and dispositions of the Company's assets.

- All disbursements of funds and all receipts must be properly and promptly recorded.

- No undisclosed or unrecorded fund or account may be established for any purposes.

- False or artificial entries must never be made in any of the books or records of the Company, or in any public record for any reason, nor should the Company's records be falsely altered in any way.

You will not take any action, for the purpose of rendering the Company's financial statements materially misleading, or to fraudulently influence, coerce, manipulate, or mislead any independent accountant engaged in the performance of an audit of the Company's financial statements.

4. Retention of Records

Legal practice requires the retention of certain records for various periods of time, particularly those relating to taxes, personnel, contracts and corporate structure. When litigation or a government investigation or audit is pending or imminent, you must not destroy any relevant

records until the matter is closed. Destruction of records to avoid disclosure in a legal proceeding or investigation may constitute a criminal offense.

C. *Conflicts of Interest*

You cannot without the Company's express written consent, engage in any employment or business activity other than for the Company. Unless expressly consented to in writing by the Company, your personal activities should not involve the use of Company property, facilities, influence or other resources, and should not reflect discredit upon the Company.

You will not engage in any activity through which you stand to benefit personally from any sale or purchase of goods and services by the Company. This provision does not apply to benefits arising out of your employment with the Company, or to ownership of equity in a publicly traded company which was purchased on the open market and represents (i) less than 1% of such company's outstanding equity and (ii) less than 5% of your equity portfolio.

Without a determination from the Board of Directors (for executive officers and Directors) or the CEO or Executive Vice President (for non-executive officers) that no conflict of interest exists, you will not engage in any activity, including acting as an employee, director, or advisor for any entity that directly or indirectly competes with Isis.

You must promptly disclose in writing any actual or potential conflicts of interest to Isis' Executive Vice President, CEO or Vice President Human Resources. Isis will review the matter, as set forth above, and communicate its position in writing.

D. *Dishonesty and Theft*

You will not knowingly:

- Engage in fraud or embezzlement affecting Company property, funds, securities or other assets; or
- Willfully damage or destroy property or materials belonging to the Company, its employees or customers.

In addition, without proper supervisory authorization, you will not knowingly:

- Remove property, material or money from the Company, its employees, or its customers for personal gain, personal use, resale or to give to another party;
- Receive property, materials or money belonging to the Company, its employees or its customers for personal gain, personal use, resale or to give to another party;
- Access, remove, publish, destroy or alter private or confidential information existing in physical Company records or electronically stored information;
- Remove, publish, destroy or alter other physical Company records or electronically stored information affecting the Company, its employees or corporate partners; or
- Copy, reprint, duplicate, or recreate in whole or in part, computer programs or related systems developed or modified by Isis personnel, or acquired from outside vendors.

E. *Insider Trading*

During the course of your employment, you may receive important information which is not yet publicly available ("inside information") about Isis or about other publicly traded companies with which the Company has business dealings. Because of your access to this information, you may be in a position to profit financially by buying or selling or in some other way dealing in Company stock or the stock of another publicly traded company. Or you may be in a position to benefit

financially or otherwise by passing this information on to some other person. Whether you personally benefit or another benefits, this is considered "insider trading" and is illegal.

You may not disclose inside information to anyone inside the Company who is not authorized to access it or to anyone outside the Company. When you have access to inside information, you may not buy or sell Isis stock regardless of the number of shares nor may you encourage or discourage others from trading on Company stock.

IV. WAIVERS FOR EXECUTIVE OFFICERS AND DIRECTORS

Any waiver of this Code of Ethics for executive officers or members of the Board of Directors must be approved by the Board of Directors and must be promptly disclosed to the Company's stockholders, including the reasons for the waiver.

V. REPORTING SUSPECTED VIOLATIONS

If you suspect accounting improprieties, violations of the law or this Code of Ethics you should immediately communicate your concern to the Vice President Human Resources, the General Counsel, the Executive Vice President or the CEO. Any one of these officers who receives such a complaint will immediately communicate the complaint to the chairman of the Audit Committee. Alternatively, you may report any such violations directly to the chairman of the Audit Committee. Any concern may be made anonymously and will be taken seriously. All parties involved in the investigation will be required to cooperate fully, maintain complete confidentiality and take no action which might be considered retaliatory.

VI. CONSEQUENCES OF VIOLATING ISIS' CODE OF ETHICS

If you violate the law, the Isis Code of Ethics or Isis' policies, you may be subject to disciplinary action, up to and including termination. If necessary, Isis may suspend your employment during an investigation into an alleged breach. Additional actions may include reassignment of work duties and limitation in future job opportunities. Isis may refer violations of law to local or federal law enforcement authorities for possible prosecution.

APPENDIX A

THE FOREIGN CORRUPT PRACTICES ACT

The Foreign Corrupt Practices Act (FCPA) prohibits U.S. companies from making improper payments or gifts to foreign officials. Company policy requires that all directors, officers, employees, agents and consultants of Isis comply with the FCPA.

A. *Definition of Foreign Official*

Under the FCPA, the term "foreign official" includes elected and appointed governmental officials, candidates for public office, foreign political parties, officers and employees of government owned or controlled enterprises, and public international organizations. When in doubt, Isis employees should consult the Company's Legal Counsel for advice on whether a potential recipient of a payment is a "foreign official."

B. *Prohibited Acts*

The following acts are prohibited by the FCPA:

1. Authorizing, paying, promising or delivering any payment, gift or favor intended to influence any foreign official on a matter within that person's responsibilities. For example, any payment to any foreign official for the purposes of obtaining or retaining sales of products or services to Isis, sales by Isis of Isis products or services, to win a bid or contract, or to obtain more favorable tax treatment is prohibited.

2. Any indirect payment to a third party if the payor knows that the third party may make a prohibited payment. For example, any payment to an Isis agent or consultant where the payor is aware or has firm belief that such agent or consultant may make an improper payment to a foreign official is prohibited. The Isis payor may not avoid this prohibition by deliberately ignoring or purposefully avoiding knowledge that a bribe may be paid.

3. Establishing any undisclosed or unrecorded "slush" funds or assets; making any false or artificial entries in company books or records; failing to keep books, records and accounts in reasonable detail to reflect accurately the handling of money and other assets; and failing to maintain internal accounting controls sufficient to verify that no improper payments have been made.

C. *Permissible Payments*

The following payments may be made:

1. Payments to a foreign official for the purpose of expediting or securing the performance of a routine governmental action. Payments for the following routine governmental actions are permissible: obtaining permits, licenses or other official documents to qualify to do business in a foreign country; processing governmental papers, such as visas and work orders; assuring police protection, mail pickup and delivery, or scheduling inspections associated with contract performance or inspections related to the transit of goods across country; and providing phone service, power and water supply, loading and unloading cargo or protecting perishable products or commodities from deterioration. Routine governmental action does not include any decision by a foreign official to encourage, to award, to continue or to modify the terms relating to any business with any Isis entity.

2. Any payment that is lawful under the written laws and regulations of the foreign country.

3. Any reasonable expenditure directly related to the promotion, demonstration or explanation of Isis products or services or the execution or performance of a contract with a foreign

government or agency, such as the travel and lodging expenses of a foreign official on a trip for such purposes.

D. *Penalties*

Violations of the anti-bribery provisions of the FCPA may result in criminal fines of up to $2,000,000 for corporations and $100,000 and five years imprisonment for individuals. Violations of the accounting provisions may result in fines of up to $2,500,000 for corporations and $1,000,000 and ten years imprisonment for individuals. Under alternative fine provisions, a violator may be fined up to twice the amount of the gain or loss resulting from a violation.

PAYMENTS AND THE FCPA

Neither Isis nor any director, officer, employee, agent or consultant of the Company will directly or indirectly make or promise illegal payments or contributions, or engage in any other illegal conduct in order to influence customers, suppliers or governmental entities, including their officials or employees, to secure or retain business, to encourage any such employees or officials to fail to perform or to perform improperly their official functions or to influence legislation, nor undertake any of the acts prohibited by the FCPA, as summarized above. Neither Isis nor any director, officer, employee, agent or consultant of the Company will submit to extortion as a condition of doing business.

QuickLinks

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-43330, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859) of Isis Pharmaceuticals, Inc. of our report dated January 26, 2004 (except for Note 12, as to which the date is March 11, 2004) with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. included in the Annual Report (Form 10-K) for the year ended December 31, 2003.

/s/ ERNST & YOUNG

San Diego, California
March 11, 2004

QuickLinks

Exhibit 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

QuickLinks -- Click here to rapidly navigate through this document

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this annual report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: March 12, 2004

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

QuickLinks

EXHIBIT 31.2

CERTIFICATION

QuickLinks -- Click here to rapidly navigate through this document

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this annual report on Form 10-K of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: March 12, 2004

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

QuickLinks

EXHIBIT 31.2

CERTIFICATION

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2003, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: March 12, 2004

/s/ STANLEY T. CROOKE, M.D., PH.D.	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D. *Chief Executive Officer*	B. Lynne Parshall, J.D. *Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

QuickLinks