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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2003

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF 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 incorporations or organization)	(I.R.S. Employer Identification No.)

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

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

(Former name, former address and former fiscal year, if changed since last report)

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.

(1) Yes ☒ No o (2) Yes ☒ No 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

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.

Common stock $.001 par value	**55,542,292 shares**
(Class)	(Outstanding at August 7, 2003)

ISIS PHARMACEUTICALS, INC.
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ISIS PHARMACEUTICALS, INC.

CONDENSED BALANCE SHEETS

(in thousands, except share data)

	June 30, 2003 (Unaudited)	December 31, 2002 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 85,318	$ 101,856
Short-term investments	170,614	187,497
Contracts receivable	2,725	14,906
Inventory	6,564	11,090
Other current assets	6,733	4,831
Total current assets	271,954	320,180
Property, plant and equipment, net	39,269	59,094
Licenses, net	29,507	30,749
Patents, net	20,644	18,904
Deposits and other assets	8,856	9,186
Long-term investments	626	570
Total assets	$ 370,856	$ 438,683
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,781	$ 5,524
Accrued compensation	3,740	3,330
Accrued liabilities	7,713	6,794
Amount due to affiliates	—	5,193

Current portion of long-term obligations	20,332	21,435
Current portion of deferred contract revenues	19,642	33,674
Total current liabilities	55,208	75,950
5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	65,221	67,893
Long-term deferred contract revenue, less current portion	12,592	14,363
Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding at June 30, 2003 and December 31, 2002	12,015	12,015
Accretion of Series B Preferred stock dividends	2,209	1,866
Common stock, $.001 par value; 100,000,000 shares authorized, 55,391,983 shares and 55,215,785 shares issued and outstanding at June 30, 2003 and December 31, 2002, respectively	55	55
Additional paid-in capital	603,364	602,101
Deferred compensation	(230)	(59)
Accumulated other comprehensive income (loss)	3,076	(608)
Accumulated deficit	(507,654)	(459,893)
Total stockholders' equity	112,835	155,477
Total liabilities and stockholders' equity	$ 370,856	$ 438,683

Note: The balance sheet at December 31, 2002 has been derived from the audited financial statements at that date.

See accompanying notes

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2003	2002	2003	2002
Revenue:				
Research and development revenue under collaborative agreements	$ 14,900	$ 17,889	$ 28,681	$ 32,603
Research and development revenue from affiliates	—	2,087	—	5,121
Licensing and royalty revenue	116	85	316	296
Total revenue	15,016	20,061	28,997	38,020
Operating expenses:				
Research and development	30,179	31,530	60,439	58,513
General and administrative	2,431	2,444	5,054	4,671
Compensation (benefit) related to stock options	123	(1,574)	132	(3,106)
Restructuring activities	1,803	—	1,803	—
Total operating expenses	34,536	32,400	67,428	60,078
Loss from operations	(19,520)	(12,339)	(38,431)	(22,058)
Other income (expenses):				
Equity in loss of affiliates	—	(3,960)	—	(9,726)
Investment income	1,167	1,892	2,803	4,036
Interest expense	(4,745)	(4,164)	(9,352)	(8,795)
Loss on investments	—	—	(2,438)	—
Loss on prepayment of debt	—	(2,294)	—	(2,294)

Net loss	(23,098)	(20,865)	(47,418)	(38,837)
Accretion of dividends on preferred stock	(172)	(335)	(343)	(670)
Net loss applicable to common stock	$ (23,270)	$ (21,200)	$ (47,761)	$ (39,507)
Basic and diluted net loss per share	$ (0.42)	$ (0.39)	$ (0.86)	$ (0.73)
Shares used in computing basic and diluted net loss per share	55,380	54,117	55,378	54,022

See accompanying notes

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF CASH FLOWS

(in thousands)

(Unaudited)

	Six Months Ended June 30,	
	2003	**2002**
Net cash used in operating activities	$ (40,308)	$ (70,777)
Investing activities:		
Purchase of short-term investments	(93,594)	(105,932)
Proceeds from the sale of short-term investments	110,578	74,560
Purchase of property, plant and equipment	(5,343)	(12,450)
Other assets	(2,481)	(2,667)
Investments in affiliates	(5,193)	(3,690)
Net cash provided from (used in) investing activities	3,967	(50,179)
Financing activities:		
Net proceeds from issuance of equity	962	6,475
Proceeds from long-term borrowings	22,116	18,513
Net proceeds from issuance of convertible debt	—	120,935
Principal payments on debt and capital lease obligations	(3,275)	(1,901)
Principal payment on prepayment of debt	—	(40,060)
Net cash provided from financing activities	19,803	103,962
Net decrease in cash and cash equivalents	(16,538)	(16,994)
Cash and cash equivalents at beginning of period	101,856	127,011
Cash and cash equivalents at end of period	$ 85,318	$ 110,017
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,931	$ 34,003
Supplemental disclosures of non-cash investing and financing activities:		
Decrease in property, plant and equipment and notes payable	$ 21,200	$ —
Decrease in inventory and deferred revenue	$ 8,750	$ —

See accompanying notes

ISIS PHARMACEUTICALS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS

June 30, 2003

(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the six month periods ended June 30, 2003 and 2002 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2002. The financial statements include all adjustments (consisting only of normal recurring adjustments), which the Company considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2002 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. Significant Accounting Policies

Revenue Recognition

The Company recognizes revenue when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenue under collaborative agreements

The Company recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. The Company defers payments received under these agreements that are related to future performance and records revenue as it is earned over the specified future performance period. The Company recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as it satisfies its performance obligations. The Company recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. The Company will recognize revenue related to milestones that are part of arrangements entered into subsequent to June 30, 2003 in accordance with *Emerging Issues Task Force Issue No. 00-21* (EITF 00-21). EITF 00-21 requires the Company to recognize revenue related to the milestones over the period of obligation. The Company records revenue from federal research grants during the period in which it incurs the related expenditures. The Company recognizes revenue from product sales as it ships the products.

As part of the Company's alliance with Eli Lilly and Company in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of June 30, 2003, the Company had drawn down $61.3 million on the $100.0 million loan. The Company discounted the $61.3 million to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time the Company entered into the loan. The Company 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. The Company accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Research and development revenue from affiliates

The Company recognized research and development revenue from affiliates as it incurred the related expenses, up to contractual limits. The Company recognized revenue related to milestones upon

completion of the milestone's performance requirement. In late 2002, the Company terminated its HepaSense and Orasense collaborations with Elan Corporation plc and as a result, the Company no longer earns revenue from these collaborations.

Licensing and royalty revenue

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

Concentration of credit risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. The Company places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. The Company invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. The Company 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

The Company considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. The Company's short-term investments have initial maturities of greater than ninety days from date of purchase. The Company classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investment in Debt and Equity Securities*. The Company 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. The cost of debt securities sold is based on the specific identification method. The Company includes gross realized gains and losses in investment income and these amounts have not been material. To date, the Company has not had any material losses related to its cash or cash equivalents. During the first quarter of 2003, the Company 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. 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 was determined to be other-than-temporary. In the second quarter of 2003, the Company recorded unrealized gains related to its

equity investments in ATL and Hybridon as a separate component of stockholders' equity, which reflected the increase in the market value of the investments since the first quarter of 2003.

Inventory Valuation

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

estimated net realizable value. Inventory includes the following categories as of June 30, 2003 and December 31, 2002, net of reserves (in thousands):

	June 30, 2003	December 31, 2002
Raw materials	$ 2,780	$ 10,186
Work-in-process	3,784	904
	$ 6,564	$ 11,090

Use of Estimates

The preparation of 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 financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-Based Employee Compensation

In April 2003, the Company implemented an employee stock option exchange program to maintain one of the Company's key assets, its employee base, in a manner that was sensitive to shareholder interests. The 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 typically were higher priced, in exchange for a lesser number of options, which typically were lower priced. Employees exchanged 2.2 million options with a weighted-average exercise price of $14.89 for 1.0 million options with an exercise price of $5.15. The new options vest over 3 years beginning on January 1, 2003 and expire on December 31, 2008. The Company accounted for the affected options using variable accounting consistent with the provisions of *Accounting Principles Board Opinion No. 25* and *Financial Accounting Standard Board Interpretation No. 44*. As a result, the Company recorded compensation expense of approximately $115,000 in the second quarter of 2003 and will continue to account for the affected options using variable accounting until all affected options have been exercised or cancelled.

The Company has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation*. Accordingly, no compensation expense, except for compensation expense primarily related to the affected options from the 2000 and 2003 exchange programs, has been recognized for the Company's stock option plans. Had compensation expense been determined consistent with SFAS 123,

the Company's net loss and basic and diluted net loss per share would have been changed to the following proforma amounts (in thousands, except per share amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2003	2002	2003	2002
Net loss applicable to common stock	$ (23,270)	$ (21,200)	$ (47,761)	$ (39,507)
Stock based compensation	2,025	(6,346)	(990)	(12,302)
Proforma net loss applicable to common stock	$ (21,245)	$ (27,546)	$ (48,751)	$ (51,809)
Earnings per share:				
Basic and diluted	$ (0.42)	$ (0.39)	$ (0.86)	$ (0.73)
Basic and diluted, proforma	$ (0.38)	$ (0.51)	$ (0.88)	$ (0.96)

For the purpose of this proforma calculation, the Company estimates the fair value of each option grant on the date of grant using the Black-Scholes option pricing model with the following assumptions for June 30, 2003 and 2002: 1) a risk free rate of 3.53% and 4.82%, respectively; 2) a dividend yield of 0% each year; 3) a volatility factor of 85.6% and 73.9%, respectively; and 4) an option life of 5.1 and 5.8 years, respectively. The weighted average fair value of options granted was $5.11 and $5.79 for the three and six months ended June 30, 2003, respectively. The weighted average fair value of options granted was $12.04 and $17.83 for the three and six months ended June 30, 2002, respectively.

Reclassification

Certain prior period amounts have been reclassified to conform to current presentation.

Impact of Recently Issued Accounting Standards

In November 2002, the Emerging Issues Task Force issued 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. EITF 00-21 is effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. The Company reviewed EITF 00-21 and determined that this issue will not have a material impact on its operating results and financial position.

In December 2002, the Financial Accounting Standards Board issued SFAS 148, *Accounting for Stock-Based Compensation—Transition and Disclosure*, effective for fiscal years ending after December 15, 2002. The rule amends SFAS 123 to provide several alternatives for adopting the stock option expense provisions of SFAS 123, as well as additional required interim financial statement disclosures. SFAS 148 does not require companies to expense stock options in current earnings. The Company has not adopted the provisions of SFAS 123 for expensing stock based compensation; however, the Company has adopted the additional interim disclosure provisions of the statement (see *Stock-Based Employee Compensation* above). The impact of the new standard is not expected to have a material impact on the results of operations or the financial position of the Company.

3. Strategic Alliances

Affiliates

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in Orasense under the equity method of accounting. Through December 2002, Orasense incurred research and development expenses, performed by Elan and the Company on Orasense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002, and the Company reacquired all rights to ISIS 104838, the compound that the collaboration had been developing. The following table presents summary results of operations for the three and six months ended June 30, 2002 for Orasense (in thousands):

	Three Months Ended June 30, 2002	Six Months Ended June 30, 2002
Revenue	$ —	$ —
Research and development expense	1,080	4,311
Net loss	$ (1,080)	(4,311)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in HepaSense under the equity method of accounting. Through December 2002, HepaSense incurred research and development expenses, performed by Elan and the Company on HepaSense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the HepaSense collaboration in 2002 and the Company reacquired all rights to ISIS 14803, the compound that the collaboration had been developing. As a result of the collaboration termination, there was no activity during the six months ended June 30, 2003. The following table presents summary results of operations for the three and six months ended June 30, 2002 for HepaSense (in thousands):

	Three Months Ended June 30, 2002	Six Months Ended June 30, 2002
Revenue	$ —	$ —
Research and development expense	3,864	7,833
Net loss	$ (3,864)	$ (7,833)

Amgen

In February 2003, the Company earned a second research milestone in its drug discovery collaboration with Amgen, which was initiated in December 2001. Amgen and the Company are collaborating to discover and develop new antisense drugs utilizing the Company's proprietary second-

generation chemistry. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration.

Lilly Oncology Collaboration

In April 2003, the Company earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin, as part of the research collaboration oncology expansion entered into in fiscal year 2002 with Lilly. ISIS 23722 is the first compound from the partnership to be selected for clinical development by Lilly.

Pantheco A/S

In May 2003, the Company entered into an amended and restated license agreement with Pantheco A/S. The amended and restated license agreement replaces the nonexclusive license agreement the Company entered with Pantheco in September 2000 and the exclusive license agreement the Company entered with Pantheco in November 1998. Under the terms of the amended and restated license agreement, the Company licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Pantheco on a limited exclusive basis to develop products. The license is restricted to a limited number of molecular targets that are subject to the Company's approval. In consideration for the license, Pantheco agreed to pay the Company royalties and milestones on any products developed under the license.

In addition, in May 2003, Pantheco A/S and Cureon A/S merged to form Santaris Pharma A/S. Prior to the merger, the Company purchased additional shares of Pantheco for $55,000 as the result of antidilution provisions in Pantheco's stock. After the merger and as of June 30, 2003, the Company's ownership interest in Santaris is 7.4%.

Ercole

In May 2003, the Company 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 parties cross-licensed their respective splicing-related intellectual property. Ercole also received a license to some of the Company's chemistry patents. The Company has taken an equity ownership in Ercole, with the initial funding in the form of convertible debt, which the companies anticipate will convert into securities Ercole issues in its next venture capital financing. The Company also has the option to make an additional equity investment in Ercole.

Lilly

In June 2003, the Company and Lilly reached a mutually beneficial renegotiation of their manufacturing relationship. Lilly waived repayment of the $21.2 million manufacturing loan it provided the Company to build the Affinitak manufacturing facility. Lilly agreed to allow the Company to use the facility to manufacture other drugs. In exchange, the Company released Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from the Company and the obligation to pay for the costs of maintaining an idle manufacturing suite.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes (ITRI) of Taiwan to identify antisense candidates targeting the coronavirus associated with Severe Acute Respiratory Syndrome (SARS). The Company is conducting the antisense drug discovery research and ITRI will provide up to $2.0 million in funding to support the collaboration, with the potential for further funding.

4. Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income*, requires the company to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three months ended, June 30,		Six months ended, June 30,	
	2003	2002	2003	2002
Comprehensive loss:				
Change in unrealized gains (losses)	$ 1,474	$ (1,445)	$ 3,684	$ (1,260)
Net loss applicable to common stock	(23,270)	(21,200)	(47,761)	(39,507)
Comprehensive loss	$ (21,796)	$ (22,645)	$ (44,077)	$ (40,767)

5. Restructuring

In November 2002, the Company discontinued its GeneTrove database product offering and reorganized the GeneTrove division. As a result, the Company 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, the Company recognized restructuring related charges of approximately $1.4 million as operating expenses in the fourth quarter of 2002. The Company did not recognize any additional GeneTrove restructuring related charges in the first six months of 2003 and expects to complete utilization of the reserve related to this restructuring by October 2003.

In April 2003, the Company initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, the Company had a small reduction in its workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, the Company incurred a one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and expects to complete the 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, which has been included in accrued liabilities at June 30, 2003 (in thousands):

	GeneTrove Severance Cost For Involuntary Employee Terminations	Affinitak Severance Cost For Involuntary Employee Terminations	Total
Balance at March 31, 2003	$ 132	$ —	$ 132
Reserve additions	—	1,803	1,803
Utilization of reserve:			
Cash	(51)	(1,102)	(1,153)
Balance at June 30, 2003	$ 81	$ 701	$ 782

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Report, this Report 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 and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, 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-Q. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our Annual Report on Form 10-K for the year ended December 31, 2002, which is on file with the U.S. Securities and Exchange Commission and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 24 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We design 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 the 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 a broad pipeline of antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including inflammatory, viral, metabolic and dermatological diseases, and cancer, and we are studying these drugs in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

Affinitak™, formerly LY900003 or ISIS 3521, 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 patients currently enrolled, but has suspended further enrollment in this study and other studies of Affinitak. Pending a review upon completion of the second Phase III trial, Lilly and we will make a decision about the future development of Affinitak. In June 2003, Lilly and we reached a mutually beneficial renegotiation of our manufacturing relationship. Lilly waived repayment of the $21.2 million manufacturing loan it provided us to build the Affinitak manufacturing facility. Lilly 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.

We currently are conducting two Phase III clinical trials for another product, alicaforsen, or ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America and Europe and we expect to complete enrollment of these trials in the first half of 2004. Alicaforsen is an antisense inhibitor of ICAM-1 (Intercellular Adhesion Molecule-1), a molecule that plays a key role in the recruitment and activation of the immune cells associated with the inflammatory response in a wide range of inflammatory and autoimmune conditions such as Crohn's disease. We are also studying alicaforsen in an enema formulation for patients with ulcerative colitis. We also have several products in Phase II and earlier stages of development.

Our GeneTrove program uses our antisense technology as a tool to provide important information about the function of genes and has automated the inital 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, such as 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. In November 2002, we announced the termination of GeneTrove's subscription database product originally added in August 2001. This resulted in a reorganization of the GeneTrove program.

Our Ibis program has invented platform technology that has the potential to revolutionize the detection and treatment of infectious disease. We are creating a sensor that can detect known and unknown infectious agents, and are working to discover small molecule drugs that work by binding to RNA. Our scientists have invented methods of identifying common binding sites in RNA that facilitate the identification of organisms or serve as targets for drug binding. We have also invented mass spectrometry-based screening methods for both diagnostic and drug discovery applications. In a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we apply our Ibis technology to develop a sensor to detect infectious agents that could be used in biological warfare attacks. We collaborate with San Diego-based Science Applications International Corporation, or SAIC, on this multi-year project funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $11.7 million for its efforts related to TIGER. In early 2002, Ibis received a three-year contract from the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, to use its technology to develop broad-

spectrum anti-infective drugs that we believe will have usefulness in national defense. The contract provides for funding of up to $2.4 million. In addition to DARPA and USAMRIID, Ibis also has research relationships with several other government entities including the United States Navy, the Federal Bureau of Investigation and the Center for Disease Control and Prevention.

Critical Accounting Policies

We prepare our 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 estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments 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 obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Antisense Therapeutics Limited, or ATL, Amgen, Chiron, Industrial Technology Research Institutes, Lilly, and Pfizer. As of June 30, 2003, we evaluated our estimates for the periods of contractual arrangements and determined that our estimates are appropriate.

We recognize revenue related to milestones upon completion of the milestone's performance requirement. During the first quarter of 2003, we earned a milestone through our research

collaboration with Amgen. In addition, during the second quarter of 2003, we earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin.

In November 2002, the Emerging Issues Task Force issued 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. EITF 00-21 is effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. We reviewed EITF 00-21 and have determined that this issue will not have a material impact on our operating results and financial positions.

We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. Occasionally, we complete the manufacturing of drugs, but our partners ask us to deliver the drug on a later date. Under these circumstances, we ensure that our obligation is complete under the terms of the manufacturing agreement in place and title has transferred to the customer before we recognize the related revenue.

As part of our Lilly alliance, Lilly provided us a $100.0 million interest free loan to fund the research collaboration. As of June 30, 2003, we had drawn down $61.3 million on the $100.0 million loan. We discounted the $61.3 million that had been drawn on the loan as of June 30, 2003 to its 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. 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, and is accounted for as deferred revenue and is recognized as revenue over the period of performance.

Additionally, we 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.

Inventory Valuation

The value at which we carry our inventory directly impacts our results of operations. Our inventories include drugs with alternative uses that are used primarily in our development activities and drugs we manufacture for our partners under contractual terms. Our inventories are stated at the lower of cost or market, cost being determined under the first-in, first-out method. We review inventories periodically and reduce our carrying value of items considered to be slow moving or obsolete to its estimated net realizable value. In the second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak to their estimated net realizable values.

Valuation of Intellectual Property

We evaluate our licenses and patent assets for impairment on a quarterly basis, and whenever indicators of impairment exist. During this process, we review our portfolio of 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 challenges or potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that we determine that an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Investments

We primarily invest our excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. We have established guidelines relative

to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends and interest rates. In determining if and when a decline in market value below amortized cost is other-than-temporary, we, together with our external portfolio managers, evaluate the market conditions, offering prices, trends of earnings, price multiples, and other key measures for our investments in debt instruments. To date, we have not had any material losses related to our cash or cash equivalents.

We also have equity investments in biotech companies where we have an ownership interest of less than 20%. 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 stock price, the financial condition and near term prospects of the issuer, and our current need for cash. When such a decline in value is deemed to be other-than-temporary, we recognize an impairment loss in the period operating results to the extent of the decline. 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, Inc. 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 was determined to be other-than-temporary. In the second quarter of 2003, we recorded unrealized gains related to our equity investments in ATL and Hybridon as a separate component of stockholders' equity, which reflected the increase in the market value of the investments since the first quarter of 2003.

Use of Estimates

In preparing our financial statements to conform with accounting principles generally accepted in the United States, we make estimates and assumptions that affect the amounts reported in our financial statements and accompanying notes. These estimates include useful lives for fixed assets for depreciation calculations, useful lives for intellectual property for amortization calculations, estimated lives for license agreements related to deferred revenue, valuation of inventory, and assumptions for valuing stock options. Actual results could differ from these estimates.

Results of Operations

Revenue

Our total revenue was $15.0 million and $29.0 million for the three and six months ended June 30, 2003, respectively, compared with $20.1 million and $38.0 million for the same periods in 2002. The decrease in revenue 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 reacquired product rights to ISIS 14803 for hepatitis C and an oral formulation of ISIS 104838 as a result of Elan's conclusion of its participation in the HepaSense and Orasense joint ventures. As a result, we did not earn revenue from these affiliates in 2003.

Under the category of research and development revenue under collaborative agreements for the three and six months ended June 30, 2003, we reported $14.9 million and $28.7 million, respectively, compared to $17.9 million and $32.6 million for the same periods in 2002. The decrease was primarily a result of drug shipments occurring in the first six months of 2002 that were absent in the same period of 2003 and the reduction in revenue associated with the clinical development of Affinitak.

Research and development revenue from affiliates for the three and six months ended June 30, 2002 consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. For the three and six months ended June 30, 2002, we recognized $2.1 million and $5.1 million, respectively, from these collaborations as revenue. During the same periods in 2003, we did not earn revenue from these collaborations as Elan concluded its participation in the joint ventures in 2002.

Our revenue from licensing activities and royalties was $116,000 and $316,000 for the three and six months ended June 30, 2003, respectively, compared to $85,000 and $296,000 for the same periods in 2002.

Operating Expenses

Total operating expenses for the three and six months ended June 30, 2003 were $34.5 million and $67.4 million, respectively, compared to $32.4 million and $60.1 million for the same periods in 2002. On a proforma basis, operating expenses, for the three and six months ended June 30, 2003 were $32.6 million and $65.5 million, respectively, compared to $34.0 million and $63.2 million for the same periods in 2002. The decrease to the proforma basis operating expenses in the second quarter ended June 30, 2003 compared to the same period in 2002 was primarily due to our implementation of an expense reduction plan in the second quarter of 2003. The increase in expense for the first half of 2003 over the same period last year was primarily due to our continued investment in our products in development and the full implementation of our research collaboration with Lilly. Proforma operating expenses, which include research and development and general and administrative expenses, but exclude compensation expense or benefit related to stock options and restructuring activities expense, provide a supplemental comparison of results of operating expenses and represent the costs of key activities and cost drivers for us. We believe that it is important to exclude compensation expense or benefit related to stock options from proforma operating expenses because it is based on the variability of our stock price rather than operations. We believe that it is important to exclude restructuring activities because these costs are directly related to a first quarter event, which was an isolated event, and should be excluded for comparability purposes and analysis of results of operations. We have provided a reconciliation of GAAP operating expenses to proforma operating expenses. Proforma operating expenses for the three and six months ended June 30, 2003 and 2002, respectively, were the following (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2003	2002	2003	2002
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 34,536	$ 32,400	$ 67,428	$ 60,078
Excluding compensation expense (benefit) related to stock options	123	(1,574)	132	(3,106)
Excluding restructuring activities	1,803	—	1,803	—

Proforma operating expenses	$ 32,610	$ 33,974	$ 65,493	$ 63,184

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis Therapeutics' program and R&D Support costs. For the three and six months ended June 30, 2003, we reported total research and development expenditures of $30.2 million and $60.4 million, respectively, compared to $31.5 million and $58.5 million for the same periods in 2002. The $1.9 million increase for the first six months in 2003 over 2002 was primarily due to our continued investment in our products advancing in development, particularly Affinitak for non-small cell lung cancer and alicaforsen for Crohn's disease, and to the full implementation of our research collaboration with Lilly.

Antisense drug discovery costs for the three and six months ended June 30, 2003 totaled $9.1 million and $19.2 million, respectively, compared to $10.7 million and $19.5 million for the same periods in 2002. The decrease of $300,000 for the six months of 2003 over 2002 was principally a result of our implementation of an expense reduction plan in the second quarter of 2003. This decrease was slightly offset by the increased gene functionalization and target validation activities to support our in-house drug discovery programs and our research collaborations with Lilly and with Amgen.

Antisense drug development expenditures totaled $13.5 million and $25.6 million for the three and six months ended June 30, 2003, respectively, compared to $13.0 million and $24.5 million for the same periods in 2002. The increase of $1.1 million for the six months in 2003 over 2002 consists of additional expenses resulting from the advancement of our pipeline. This advancement includes the costs related to the Phase III trial of Affinitak for non-small cell lung cancer and two Phase III trials of alicaforsen for Crohn's disease, with the second trial initiated in June 2002.

Expenditures related to Affinitak for the three and six months ended June 30, 2003 were $4.3 million and $7.2 million, respectively, compared to $4.1 million and $6.5 million for the same periods of 2002. The increase of $700,000 for the first six months of 2003 over 2002 was primarily due to costs related to the final phases of our Phase III trial and $3.4 million of capitalized costs related to preparing for the commercial manufacture of Affinitak. These costs were reimbursed by Lilly and the reimbursement was recorded as revenue under collaborative agreements. Costs related to the final phases of our Phase III trial primarily occurred in the first quarter of 2003 with minimal amounts incurred in the second quarter of 2003. In March 2003, we announced the results of Affinitak for the treatment of non-small cell lung cancer. In this trial, we observed no difference in overall survival of those patients who received Affinitak plus a standard chemotherapy regimen compared to those patients who received the standard chemotherapy alone. Based on these results, we will not file an NDA for Affinitak in 2003. In April 2003, we initiated a restructuring of the company in response to the disappointing results from this 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 one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and we expect to complete the utilization of the reserve related to this restructuring in the fourth quarter of 2003. As a result of disappointing results from the first Phase III trial of Affinitak and no NDA filing in 2003, we expect a decrease in total Affinitak related expenses for the 2003 year compared to 2002.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $1.8 million and $3.6 million for the three and six months ended June 30, 2003, respectively, compared to $1.8 million and $3.2 million for the same periods of 2002. The increase of $400,000 for the six months of 2003 over 2002 is a result of the initiation of our second Phase III trial in June 2002 in Europe.

Expenditures related to our other products in development totaled $8.7 million and $13.6 million for the three and six months ended June 30, 2003, respectively, compared to $8.2 million and $13.6 million for the same periods of 2002. For the six months of 2003 over 2002, our expenses decreased on our early stage products. This decrease was offset by increased expenses related to increased enrollment in Phase II trials.

Ibis expenditures for the three and six months ended June 30, 2003 were $2.3 million and $4.9 million, respectively, compared to $2.2 million and $4.2 million for the same periods in 2002. The $700,000 increase for the six months of 2003 over 2002 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 costs for the three and six months ended June 30, 2003 were $5.1 million and $10.7 million, respectively, compared to $5.7 million and $10.3 million for the same periods in 2002. The $600,000 decrease for the three months ended June 30, 2003 over the same period of 2002 is primarily due to our planned expense reduction in the second quarter of 2003. The $400,000 increase for the six months of 2003 over 2002 is a direct result of increases in our research and development efforts to prepare for the manufacture and commercialization of Affinitak in the first quarter of 2003. This increase was partially offset by our planned expense reductions. While we work to control R&D

Support costs, we expect that they will be directly related to fluctuations in our research and development expenses.

General and administration expenses for the three and six months ended June 30, 2003 were $2.4 million and $5.1 million, respectively, compared to $2.4 million and $4.7 million for the same periods in 2002. The $400,000 increase for the six months of 2003 over 2002 was primarily a result of an increase in employees and related benefits in the first quarter of 2003. As a result of the restructuring in April 2003, we reduced the number of employees to levels comparable to the first six months of 2002.

Compensation expense for the three and six months ended June 30, 2003 was $123,000 and $132,000, respectively, which primarily consisted of compensation expense related to stock options associated with the employee stock option exchange program initiated in April 2003 and stock options granted to consultants, which we accounted for in accordance with EITF 96-18. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with *Accounting Principles Board Opinion No. 25* and *Financial Accounting Standard Board Interpretation No. 44*. In the same periods in 2002, we reported compensation benefit of $1.6 million and $3.1 million, which primarily represented the reversal of previously recorded compensation expense related to stock options accounted for as variable stock options. This benefit was associated with the option exchange program we offered to non-officer employees in January 2000. These variable stock options were either exercised or cancelled by December 31, 2002.

In the second quarter of 2003, we recorded a one-time restructuring charge of $1.8 million related to our expense reduction plan, which included a small reduction in our workforce. There were no restructuring charges in the same period of 2002.

Equity in Loss of Affiliates

We used the equity method of accounting for our investments in the Orasense and HepaSense joint ventures in which we own 80.1% and Elan owns 19.9%. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense under equity in loss of affiliates. In 2002, Elan concluded its participation in the associated collaborations and as a result, we did not recognize any equity in loss of affiliates for the three and six months ended June 30, 2003. This compares to $4.0 million and $9.7 million for the respective periods in 2002.

Investment Income

Investment income for the three and six months ended June 30, 2003 totaled $1.2 million and $2.8 million, respectively, compared to $1.9 million and $4.0 million for the same periods in 2002. The $1.2 million decrease in investment income for the first six months in 2003 over 2002 is primarily due to our lower average cash balance in the first half of 2003 compared to the first half of 2002. In addition, our investment income was affected by the decline in interest rates as a result of current market conditions.

Interest Expense

Interest expense for the three and six months ended June 30, 2003 totaled $4.7 million and $9.4 million, respectively, compared to $4.2 million and $8.8 million for the same periods in 2002. The effect of a higher debt balance as of June 30, 2003 compared to June 30, 2002 was primarily offset by a decrease in the average interest rate on our debt. The decrease in the average interest rate, which resulted in a net interest savings, is primarily due to the retirement, in May 2002 and July 2002, of higher interest rate debt with the proceeds from the issuance, in May 2002, of our $5^1/_2$% convertible subordinated notes due 2009.

Net Loss Applicable to Common Stock

For the three and six months ended June 30, 2003, we reported a net loss applicable to common stock of $23.3 million and $47.8 million, respectively, which included $172,000 and $343,000 of accreted dividends on preferred stock, respectively. Our net loss applicable to common stock was $21.2 million and $39.5 million for the three and six months ended June 30, 2002, respectively, which included $335,000 and $670,000 of accreted dividends on preferred stock, respectively. The net loss applicable to common stock for the six months ended June 30, 2003 included a non-cash loss on investments of $2.4 million related to the other-than-temporary impairment of our investments in ATL and Hybridon.

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 June 30, 2003, we have earned approximately $379.5 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 $588.3 million from the sale of equity securities. We have borrowed approximately $312.7 million under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2003, we had cash, cash equivalents and short-term investments totaling $255.9 million and working capital of $216.7 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 decreases in our cash, cash equivalents and short-term investments and working capital are due primarily to cash used to fund our operations, to purchase property, plant, and equipment and to pay our debt and capital lease obligations.

As of June 30, 2003, our debt obligations totaled $232.0 million, compared to $242.6 million at December 31, 2002. Our debt obligations include long-term and current deferred contract revenue and contractual obligations that represent our payment obligations. The decrease was primarily due to the renegotiation of our manufacturing relationship with Lilly, including 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 a note payable to Abbott Laboratories and we repaid certain of our capital leases. The decreases were offset by the additional draw downs from the $100.0 million interest-free loan from Lilly, which we discounted to their present value by imputing interest on the amount at 20% and accreting to its face value over their terms by recording interest expense and by the accrued interest on our convertible debt facility with Elan. 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 as long as the terms remain commercially attractive. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at June 30, 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. The following table summarizes our contractual obligations as of June 30, 2003. The table provides a breakdown of when

obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table.

	Payments Due by Period (in thousands)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Convertible Partner Debt	$ 91,475	$ 16,200	$ 75,275	$ —	$ —

5.5% Convertible Subordinated Notes	$ 125,000	$ —	$ —	$ —	$ 125,000
Standard Operating Debt	$ 7,810	$ 726	$ 1,452	$ 5,632	$ —
Capital Lease Obligations	$ 7,664	$ 3,534	$ 4,067	$ 63	$ —
Operating Leases	$ 13,699	$ 2,684	$ 4,580	$ 3,488	$ 2,947

Our contractual obligations are composed primarily of publicly traded convertible debt and partner debt that we can repay on favorable terms with equity at our option. Convertible partner debt includes 1) the interest-free loan Lilly made available to us to fund the joint research collaboration; 2) the convertible promissory note provided by Elan to us in conjunction with the Orasense joint venture; and 3) the convertible debt provided by Boehringer Ingelheim International GmbH, or BI, associated with the collaborative agreement between the two companies.

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 drawdowns by us. As of June 30, 2003, we had drawn down $61.3 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 are accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance. At June 30, 2003, the balance in long-term obligations was $39.9 million and the balance in deferred revenue was $21.4 million.

In April 1999, in conjunction with the Orasense joint venture, Elan made available to us an $18.4 million line of credit evidenced by a convertible promissory note. The terms of the convertible promissory note provide for interest at 12% per annum, compounded semi-annually, maturing April 19, 2005. No principal or interest payments are required until the end of the loan. The loan may be prepaid by us at any time, at our option, in whole or in part, in cash or in common stock at a price equal to the average market value of the common stock for the 60 trading days ending two business days prior to the date of prepayment. At any time prior to maturity, Elan may convert all or any portion of the loan outstanding into the number of shares of our common stock. Elan's conversion price for each amount we drew on the line of credit was set at the time we drew such amount. As of June 30, 2003, Elan's weighted average conversion price for the outstanding debt was $16.63 per share. The balance under this borrowing facility, including accrued interest, as of June 30, 2003 was $7.6 million. We cannot borrow any additional principal under this promissory note.

In 1996 and 1997, we borrowed a total of $22.6 million under a $40.0 million line of credit made available under the terms of our collaborative agreement with BI. The borrowed funds were used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and range from 8.36% to 8.46%. Interest payments are due twice each year with principal repayment due seven years after the advance date. The principal may be repaid in cash or stock, at our option. If we elect to repay the loan in shares of our common stock, repayment will be

made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of June 30, 2003 was $22.6 million.

The 5 1/2% convertible subordinated notes are due May 2009 and interest on these notes is payable on a semi-annual basis. The notes are convertible by its holders into shares of our common stock at a conversion price of $16.625 per share. At June 30, 2003, the principal balance on this debt was $125.0 million.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this Form 10-Q, 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 such receipt could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that could have a similar negative impact.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or 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, are not suitable for commercial use, or if additional testing is required to demonstrate such suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. 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.

If the market does not accept our products, we are not likely to generate significant revenues or become profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, 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 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 of our Hepatitis C research collaboration with Merck at the end of May 2003, 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.

Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly with respect to ISIS 23722, the antisense inhibitor to survivin. If any of these pharmaceutical company partners were to stop funding and/or developing these drug candidates, 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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

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

In addition, the disappointing results of our recently completed 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.

If our GeneTrove program cannot market its products and services as planned, we could lose our investment in this technology.

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

For example, in November 2002, we terminated our GeneTrove database product offering and reorganized our GeneTrove program. Consequently, we incurred a one-time charge of approximately $1.4 million associated with the restructuring during the fourth quarter of 2002.

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 June 30, 2003, our accumulated losses were approximately $507.7 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.

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

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments as of June 30, 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 the marketing of our target validation service and licensing program; 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. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale. We have a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which 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 we fail to compete effectively, our products will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

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

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

If we 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 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 United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

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

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 2004.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in specific clinical trials, including the recently announced Phase III Affinitak results, may make it more challenging to recruit and retain qualified scientific personnel.

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 convertible notes. During the 12 months preceding June 30, 2003, the market price of our common stock has ranged from $2.50 to $11.86 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 $66^{2}/_{3}$% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, 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 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES OF MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. 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 4. CONTROLS AND PROCEDURES

For the period ended June 30, 2003, an evaluation was performed under the supervision and with the participation of our management, including the Chief Executive Officer (CEO) and the Chief Financial Officer (CFO), of the effectiveness of the design and operation of our disclosure controls and procedures. Based on that evaluation, our management, including the CEO and CFO, concluded that our disclosure controls and procedures were effective as of June 30, 2003. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2003.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable

ITEM 2. CHANGES IN SECURITIES

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

On June 10, 2003, the Company's Annual Meeting of Stockholders was held in Carlsbad, California for the following purposes:

(1) To elect two (2) directors to serve as Class III directors of the Company. For Director number one, Christopher F. O. Gabrieli, the number of votes for and abstaining was 41,950,446 and 4,521,626, respectively. For Director number two, Frederick T. Muto, the number of votes for and abstaining was 45,933,702 and 538,370, respectively. In addition to the Class III directors elected at the 2003 Annual Meeting of Stockholders, Stanley T. Crooke, John C. Reed and Mark B. Skaletsky will continue to serve as our Class I directors and Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender will continue to serve as our Class II directors.

(2) To ratify the appointment of Ernst & Young LLP as the Company's independent auditors for the fiscal year ending December 31, 2003. The number of votes for, against and abstaining was 45,760,156, 623,312 and 88,603, respectively.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number	Description of Document
10.1—	Waiver and Release Agreement dated June 5, 2003 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).
10.2—	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).
10.3—	Initial Collaboration Agreement dated June 23, 2003 between the Registrant and Industrial Technology Research Institutes (with certain confidential information deleted).
10.4—	Form of Severance Agreement dated April 2003 entered into between the Registrant and its executive officers and certain key employees, together with related schedule.
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.
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.
32.1—	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

b. Reports on Form 8-K

On May 8, 2003, the Registrant filed a report on Form 8-K for the announcement of its first quarter results and the related press release dated May 8, 2003.

On August 5, 2003, the Registrant filed a report on Form 8-K for the announcement of its second quarter results and the related press release dated August 5, 2003.

Isis Pharmaceuticals, Inc.
(Registrant)

SIGNATURES

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)	August 13, 2003
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 13, 2003

QuickLinks

Exhibit 10.1

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24

WAIVER AND RELEASE AGREEMENT

This Waiver and Release Agreement (the "Release") is made and entered into effective as of June 5, 2003 between Eli Lilly and Company, having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285 ("Lilly"), and Isis Pharmaceuticals, Inc., having its principal place of business at Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, CA 92008 ("Isis").

RECITALS

1. Lilly and Isis are parties to a Revised and Restated ISIS 3521 Supply Agreement (the "Supply Agreement") and a Loan Agreement (the "Loan Agreement"), both dated as of September 30, 2002.

2. Both parties wish to terminate certain of their obligations and rights under these agreements, as set for below.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants and promises contained in this Agreement, the parties, intending to be fully bound, agree as follows:

ARTICLE I
TERMINATION

1.1 The parties agree that both the Supply Agreement, including the MRD and the Quality Agreement (both as defined in the Supply Agreement), and the Loan Agreement, including the Promissory Note (as defined in the Loan Agreement) are hereby terminated, effective as of the date first written above, and neither party shall have any further rights, duties or obligations, monetary or otherwise, under either the Loan Agreement or the Supply Agreement, except as expressly set forth herein. Without limiting the inclusiveness of this Section 1.1, the parties specifically agree that the audit rights provided to Lilly in Sections 3.06 of the Loan Agreement and 5.6 of the Supply Agreement are terminated and do not survive.

1.2 The parties have entered into a Revised Clinical Quality Agreement, which is attached hereto as Exhibit C (the "Quality Agreement"). This Quality Agreement shall remain in effect until the earliest of the following occurs: (i) no further obligations remain under the Quality Agreement; (ii) the Development and License Agreement between the parties dated August 14, 2001 is terminated; or (iii) the Quality Agreement is superseded.

1.3 Notwithstanding Section 1.1 above, or any contradictory provision in the Loan Agreement, only Section 9.10, Confidentiality, of the Loan Agreement shall survive termination:

1.4 Notwithstanding Section 1.1 above, or any contradictory provision in the Supply Agreement, only the following provisions of the Supply Agreement shall survive termination:

(a) Section 4.8, Documentation and Record Keeping

(b) Sections 9.4(b) and (c), Testing

(c) Section 11.1, Recalls

(d) Article 12, Indemnification and Insurance

(e) Article 14, Damage Limitations

(f) Section 15.8, Entire Agreement

(g) The clinical Quality Agreement dated November 13, 2001

ARTICLE II
WAIVER AND RELEASE

2.1 Lilly does hereby release and discharge Isis of and from its obligation to repay the Debt under the Loan Agreement, and waives and releases any right to limit the use of the Dedicated Facility.

2.2 Lilly does hereby release and discharge Isis of and from its obligation to manufacture and supply API under the Supply Agreement.

2.3 Isis does hereby release and discharge Lilly of and from its obligation to purchase API under the Supply Agreement.

2.4 Isis does hereby release and discharge Lilly of and from its obligation to make payments for Idle Capacity Costs under Section 5.5 of the Supply Agreement, or to make any other payments whatsoever under the Supply Agreement, except as specifically set out in Article III below.

ARTICLE III
ADDITIONAL COVENANTS

The parties to this Release hereby additionally agree and covenant that:

3.1 All outstanding and currently accrued payments due from either party to the other under the Loan Agreement and the Supply Agreement, including payments under Section 2.02 of the Loan Agreement and Section 3.1(f) of the Supply Agreement, are hereby settled in their entirety for the sum of [***] to be paid by Lilly to Isis via wire transfer within ten (10) days of the effective date of this Release in accordance with the instructions attached hereto as Exhibit A. Upon receipt of such payment, Isis will have no further claim against Lilly for any payments whatsoever under the Loan Agreement or the Supply Agreement. Lilly specifically waives any rights to reimbursement of the [***] prepayment for raw materials made to Isis under Section 5.1(a) of the Supply Agreement, and further agrees that Isis has full title to and ownership of the raw materials, with the exception of certain raw materials to be returned to Lilly (as specified below), with no restriction on use thereof and no requirement to account to Lilly therefore. Isis will return to Lilly the raw materials listed on Exhibit B, and hereby transfers to Lilly full title to and ownership of these materials, with no restriction on use thereof and no requirement to account to Isis therefore.

3.2 To the extent that Isis' obligations under the Quality Agreement have been agreed to under the Affinitak Development Plan, Lilly will have compensated Isis for such obligations under Section 2 of Amendment Number One to the Development and License Agreement. If an Isis obligation arises under the Quality Agreement that is not outlined in the Affinitak Development Plan, the Parties will promptly agree to an appropriate performance plan and budget to address such obligation, which will be approved by a designated representative(s) of each party. Without limiting the inclusiveness of the foregoing, the Parties agree that the following obligations are not outlined in the Affinitak Development Plan: (i) obligations under the Quality Agreement that arise after the [***]th day following the delivery to Lilly of the data generated as a result of the [***] drug Product stability testing as contemplated by the Development Plan, except those obligations that arise under Section 2, 4, 9, 10 or 12 of the Quality Agreement; (ii) actions required to be taken by Isis under Section 7 of the Quality Agreement as requested by Lilly and beyond those which Isis is required to complete per Isis procedures and applicable law for out of specification results and/or confirmed stability failures; (iii) obligations arising from regulatory inspections or inquiries under Sections 9 and 10 of the Quality Agreement; and (iv) obligations incurred at the request of Lilly under Section 16 of the Quality Agreement that result from [***].

3.3 The parties acknowledge and admit that no other representation, promise or agreement of any nature whatsoever, has been made to them, and that this Release contains the entire agreement between the parties and that all terms of this Release are binding upon them. This Release shall

supersede any prior agreements, written or oral, between the parties hereto related to the subject matter of this Release.

3.4 This Release may not be modified or amended except by an instrument in writing executed and delivered by each of the parties hereto.

3.5 The respective representations and warranties of the parties contained herein shall survive the effective date of this Settlement Agreement and Release and shall continue until the discharge of all obligations pursuant to this Agreement.

3.6 This Release shall be governed by and construed and enforced in accordance with the laws of the State of Delaware, without reference to the rules in Delaware or elsewhere governing choice of law.

3.7 This Release shall be binding on and shall inure to the benefit of the parties, their respective successors and assigns.

3.8 This Release is entered into for the sole benefit of Isis and Lilly. Nothing contained herein shall be construed or interpreted to create any third party beneficiary contract rights in any other person.

3.9 This Release may be executed in counterparts, copies of which may be transmitted by facsimile, and a facsimile copy of an executed counterpart shall be sufficient evidence of the executed counterpart. The rights and obligations of each to the other shall be effective upon their execution of this Release.

IN WITNESS WHEREOF, and intending to be legally bound hereby, we have hereunto set our hands this 5th day of June, 2003.

ELI LILLY AND COMPANY

By: /s/ CHARLES E. GOLDEN

Title: CFO, Executive Vice President

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

Title: CFO, Executive Vice President

Exhibit A
Account Information
[***]

Exhibit B
Raw Materials to be Returned to Lilly

Isis will ship to Lilly [***] kilograms each of the following [***]:

[***]

[***]

[***]

Exhibit C
Quality Agreement
[***]

QuickLinks

WAIVER AND RELEASE AGREEMENT

Exhibit 10.2

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24

AMENDMENT NUMBER ONE TO
DEVELOPMENT AND LICENSE AGREEMENT
BETWEEN
ELI LILLY AND COMPANY AND
ISIS PHARMACEUTICALS, INC.

This Amendment Number One (the "Amendment") to the Development and License Agreement between Eli Lilly and Company ("Lilly") and ISIS Pharmaceuticals, Inc. ("ISIS"), effective August 14, 2001 (the "Agreement") is made effective as of June 5, 2003.

1. The parties hereby mutually agree to amend the Agreement as follows:

   Exhibit C, Development Plan, to the Agreement is hereby deleted in its entirety and replaced with the revised Exhibit C attached hereto.

2. In consideration of the activities outlined in the revised Development Plan, and in satisfaction of all outstanding invoices and currently accrued payment due from either party to the other related to the Agreement, Lilly agrees to pay ISIS the sum of [***] to be paid by Lilly to ISIS via wire transfer within ten (10) days of the effective date of this Amendment. This payment constitutes the entire compensation for the Development Plan. Upon receipt of such payment, Isis will have no further claim against Lilly for any payment whatsoever under either the original Exhibit C to the Agreement or the amended Exhibit C attached hereto. The parties agree that ISIS will not undertake any additional activity related to the Agreement without the prior written consent of Lilly. ISIS waives its right to payment or reimbursement for any such activities undertaken without Lilly's prior consent.

IN WITNESS WHEREOF, each of Lilly and ISIS have caused this Amendment to be signed by its duly authorized representatives.

ELI LILLY AND COMPANY		ISIS PHARMACEUTICALS, INC.	
By:	/s/ CHARLES E. GOLDEN	By:	/s/ B. LYNNE PARSHALL
Name:	Charles E. Golden	Name:	B. Lynne Parshall
Date:	June 3, 2003	Date:	June 5, 2003

Exhibit C
Development Plan
[***]

Exhibit 10.3

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24

INITIAL COLLABORATION AGREEMENT

THIS INITIAL COLLABORATION AGREEMENT ("Agreement") is made and entered into effective as of June 23, 2003 (the "Effective Date"), by and between Industrial Technology Research Institutes ("ITRI"), located at 195 Chung-Hsing Road, Sec. 4, Chutung, Hsinchu, Taiwan 310, R.O.C., and ISIS PHARMACEUTICALS, INC., having principal offices at 2292 Faraday Avenue, Carlsbad CA 92008 ("Isis"). ITRI and Isis each may be referred to herein individually as a "Party," or collectively as the "Parties."

Isis will conduct the First Stage Research Plan to identify and initially develop antisense drugs to treat SARS. Isis and ITRI will negotiate an agreement for the continued development and commercialization of SARS antisense drugs identified under the First Stage Research Plan.

The Parties agree as follows:

ARTICLE 1—DEFINITIONS

Capitalized terms used in this Agreement have the meanings set forth in Appendix 1.

ARTICLE 2—
COLLABORATION

Section 2.1 **First Stage Research Plan.** Isis' responsibilities for research and development under this Initial Collaboration Agreement are set forth in Appendix 2.1, the "First Stage Research Plan".

Section 2.2 **Future Collaboration Agreement.** Isis and ITRI will negotiate in good faith to enter, no later than [***], an agreement for the continuation of SARS drug research and development beyond that described in the First Stage Research Plan, with consideration to be given to the terms attached as Appendix 2.2. Payments made by ITRI under Section 3.1 of this Initial Collaboration Agreement will be credited against the research payments due under the future Collaboration Agreement. To the extent necessary, the future Collaboration Agreement will be adjusted to account for work performed under the First Stage Research Plan of this Initial Collaboration Agreement.

Section 2.3 **Rights If Future Collaboration Agreement Not Consummated.** If Isis and ITRI do not enter the future Collaboration Agreement described in Section 2.2, the Parties agree as follows; in addition to any rights obtained through this agreement that survive,

2.3.1 Isis will provide to ITRI data on the SARS antisense inhibitors developed under the First Stage Research Plan, and will train ITRI scientists to use antisense target validation know-how, including RNAi technology, for research use only in ITRI laboratories. Information provided hereunder and generated by ITRI's antisense program may not be made commercially available by ITRI for non-research purposes. ITRI will be responsible for the cost of the training of ITRI's scientists pursuant to a plan and budget to be developed and agreed upon between Isis and ITRI.

2.3.2 Isis will grant to ITRI or its Taiwanese designee the right to market and distribute an antisense SARS drug arising out of the First Stage Research Plan in Taiwan, provided that such drug is purchased from Isis or an Isis authorized manufacturer. Isis will provide to ITRI or its Taiwanese designee any data from the First Stage Research Plan required by ITRI or its Taiwanese designee to market and distribute such antisense SARS drug in Taiwan. If requested by ITRI prior to the completion of the First Stage Research Plan, Isis and ITRI will negotiate an agreement under which Isis will on reasonable terms and conditions (i) transfer to ITRI, for its sole use,

technology to manufacture antisense drugs for SARS; and/or (ii) manufacture antisense SARS drugs that result from the First Stage Research Plan for the Taiwan Government for emergency use.

ARTICLE 3—
FINANCIAL PROVISIONS

Section 3.1 **Funding of the First Stage Research Plan.**

3.1.1 Initial Funding. ITRI will pay to Isis initial funding of [***] (U.S.) upon signing this Agreement.

3.1.2 Milestone Payments by ITRI. ITRI will pay to Isis milestone payments as follows:

[***] (U.S.) within [***] days of the receipt by ITRI of both Isis's invoice and the report concerning Isis's identification of an antisense drug which inhibits replication of SARS coronavirus in a cell-based assay, with an IC50 of less than [***] micromolar; and,

[***] (U.S.) within [***] days of the receipt by ITRI of both Isis's invoice and the report concerning Isis's completion of its obligations under the First Stage Research Plan.

ARTICLE 4—
CONFIDENTIALITY

Section 4.1 **Disclosure and Use Restriction.** All Confidential Information disclosed by one party to the other party hereunder shall be maintained in confidence by the receiving party and shall not be disclosed to a non-party or used for any purpose except as set forth herein without the prior written consent of the disclosing party, except to the extent that such Confidential Information:

(a) is disclosed to governmental or other regulatory agencies by either party in order to obtain patents or to gain approval to conduct clinical trials or to market antisense SARS drugs, but such disclosure may be only to the extent reasonably necessary to obtain patents or authorizations;

(b) is deemed necessary by either Party to be disclosed to sublicensees, agents, consultants, and/or other third parties for the development, manufacturing and/or marketing of antisense SARS drugs (or for such parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such third parties agree to be bound by the confidentiality obligations contained this Agreement, *provided* the term of confidentiality for such third parties shall be no less than [***] years; or

(c) is required to be disclosed by law or court order, or is required to be disclosed by regulation or order of a competent authority (including any regulatory or governmental body or department or securities exchange or court or tribunal), provided that notice is promptly delivered to the other party in order to provide an opportunity to challenge or limit the disclosure obligations.

Section 4.2 **Period of Confidentiality.** The obligations with respect to maintaining the confidentiality of the Confidential Information provided under this Agreement shall be in effect for [***] years from the Effective date.

Section 4.3 **Press Releases.** Press releases or other similar public communication by either Party relating to this Agreement, will be approved in advance by the other Party, which approval will not be unreasonably withheld or delayed, except for those communications required by law, disclosures of information for which consent has previously been obtained, and information of a similar nature to that which has been previously disclosed publicly with respect to this Agreement, each of which will not require advance approval, but will be provided to the other Party as soon as practicable after the release or communication thereof.

ARTICLE 5—
INTELLECTUAL PROPERTY

Section 5.1 **Intellectual Property Ownership.** Ownership of inventions conceived or reduced to practice as part of the performance of this Agreement will be determined in accordance with the rules of inventorship under United States patent laws. [***] Either ITRI or Isis shall have the full right to use, make, license or otherwise dispose of its rights without prior consent of the other owner under such Joint Patents.

Section 5.2 **Access to Inventions.** Isis grants to ITRI a non-exclusive, sublicensable, [***] license to any invention invented by Isis as part of the performance of this Agreement, such license solely to develop or commercialize, in [***] only, a SARS antisense drug arising out of the First Stage Research Plan. ITRI grants to Isis a non-exclusive, sublicensable, [***] license to any invention invented by ITRI as part of the performance of this Agreement, such license solely to develop or commercialize, [***], a SARS antisense drug arising out of the First Stage Research Plan.

Section 5.3 **Prosecution of Joint Patents.** In general**,** Isis will have the first right to file, in both parties name, and at shared expense, to prosecute and maintain any Joint Patents. *However*, if either party elects not to pursue the filing, prosecution or maintenance of a Joint Patent in a specific country, or take any other action with respect to such Joint Patent that is necessary to establish or preserve rights thereto in that country, that party will so notify the other party promptly in writing and in good time to enable the other party to meet any deadlines by which an action must be taken to establish or preserve any rights in such Joint Patent in that country, and the other party will have the right to file, prosecute or maintain such Joint Patent, at its expense but in the joint names of both parties.

ARTICLE 6—
TERM AND TERMINATION

Section 6.1 **Term.** Unless earlier terminated in accordance with the provisions of this Article 6, the term of this Agreement (the "Term") will commence upon the Effective Date and will continue until the completion of the First Stage Research Plan, and receipt by Isis of all payments due under Sections 3.1.1 and 3.1.2.

Section 6.2 **Termination for Material Breach.** Either Party may terminate this Agreement if the other Party commits any other material breach of this Agreement and fails to cure such breach within 90 calendar days after receipt of written notice of such breach from the non-breaching Party (or, if such breach cannot be cured within such 90-day period, if the Party in breach does not diligently pursue cure of such breach). *provided, however*, that in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be stayed until such time as the dispute is resolved. Termination for material breach is without prejudice to any rights or remedies otherwise available to the non-breaching Party.

Section 6.3 **Surviving Obligations.** Articles 4, 5, 7, 8 and 9 and this Section 6.4 will survive expiration or termination of this Agreement for any reason.

Section 6.4 **Surviving Licenses.** Licenses or sublicenses granted under Section 5.2 of this Agreement will survive expiration or termination of this Agreement for any reason.

ARTICLE 7—
INDEMNIFICATION

Section 7.1 **Indemnification.** Each party is responsible for its own acts and omissions relating to this Agreement and any materials transferred in connection with this Agreement. Each party agrees to indemnify, defend, and hold each other harmless from and against any liability, damages, costs or

expenses (including attorneys' fees) resulting from any claim, demand, loss, injury, or liability of any kind or nature arising from its (a) breach of this Agreement; or (b) negligent or intentionally tortious acts or omissions in connection with the performance of this Agreement.

ARTICLE 8—
WARRANTIES

Section 8.1 **DISCLAIMER OF WARRANTY.** ISIS MAKES NO REPRESENTATIONS AND GRANTS NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ISIS SPECIFICALLY DISCLAIMS ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 9—
MISCELLANEOUS

Section 9.1 **Assignment.** Without the prior written consent of the other Party hereto, neither Party will transfer or assign this Agreement or any of its rights or duties hereunder; *provided, however,* that Isis may assign or transfer this Agreement or any of its rights or obligations hereunder without the consent of ITRI to any third party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets to which this Agreement relates.

Section 9.2 **Severability.** If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, all remaining portions shall remain in full force and effect.

Section 9.3 **Governing Law.** This Agreement will be governed by and construed in accordance with the laws of New York without reference to any rules of conflicts of laws.

Section 9.4 **Notices.** All notices or other communications that are required hereunder will be in writing and sent by facsimile (and confirmed by overnight courier), or sent by internationally-recognized overnight courier, addressed as follows:

If to ITRI, to:

Industrial Technology Research Institutes
195 Chung-Hsing Road, Sec. 4
Chutung, Hsinchu, Taiwan 310, R.O.C

Attention: Dr. Chungcheng Liu
Facsimile: 886-03-5820445

If to Isis, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: Executive Vice President
Facsimile: (760) 603-4650

with a copy to:

Attention: General Counsel
Facsimile: (760) 268-4922

Each Party may change its address, addressee or other information by written notice to the other Party as provided above. Any notice or communication will be deemed to have been given (i) when sent, if by facsimile on a business day, or (ii) on the second business day after dispatch, if sent by courier.

Section 9.5 **Entire Agreement; Modifications.** This Agreement sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof and supercedes all prior agreements, whether written or oral. Any amendment or modification to this Agreement must be duly executed by authorized representatives of both Parties.

Section 9.6 **Construction.** Appendices to this Agreement, or added hereto according to the terms of this Agreement, are part of this Agreement.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

INDUSTRIAL TECHNOLOGY RESEARCH INSTITUTE

Signed By: /s/ JOHNSEE LEE, PH.D

Johnsee Lee, Ph.D
Executive Vice President of ITRI
and General Director of BMEC

ISIS PHARMACEUTICALS, INC.

Signed By: /s/ STANLEY T. CROOKE, M.D., PH.D.

Stanley T. Crooke, M.D., Ph.D.
CEO

APPENDIX 1
Definitions

"Confidential Information" means any and all information and data, including without limitation all scientific, preclinical, clinical, regulatory, manufacturing, marketing, financial and commercial information *and* data, whether communicated in writing or orally or by any other method, which is provided by one party to the other party in connection with this Agreement, unless such information

(a) was already known to the receiving Party, other than under an obligation of confidentiality or non-use, at the time of disclosure to such receiving Party;

(b) is properly in the public domain;

(c) became generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or otherwise became part of the public domain, after its disclosure to such receiving Party through no fault of the receiving Party;

was independently discovered or developed prior to disclosure by such receiving Party, as evidenced by their written records, without the use of Confidential Information belonging to the Party that Controls such information and know-how.

"First Stage Research Plan" means the Parties' initial development plan for antisense SARS drugs, as set forth in Appendix 2.1.

"Joint Patent" has the meaning set forth in Section 5.1.

APPENDIX 2.1
FIRST STAGE RESEARCH PLAN

[***]

APPENDIX 2.2
Taiwan
SARS Research and Development Collaboration Term-Sheet

[***]

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 10.4

April , 2003

VIA HAND DELIVERY

[Employee Name]
[Title]
Isis Pharmaceuticals, Inc.
2292 Faraday Ave.
Carlsbad, CA 92008

Dear [FirstName]:

Isis Pharmaceuticals, Inc. ("Isis") is pleased to offer you certain severance benefits in light of your contribution to Isis. As Isis has no policy or procedure requiring such benefits, we request that you keep the terms and conditions of this letter agreement confidential.

In the event that your employment is terminated without "cause" (as defined herein) by Isis on or before December 31, 2005 (the "Severance Period"), you will be eligible to receive a severance payment equal to a minimum of [number (#)] months of your then current base salary, less payroll deductions and withholdings. For purposes of this letter agreement, "cause" will be defined as follows: (i) engaging or in any manner participating in any activity which is competitive with or intentionally injurious to Isis or which violates any provision of the Proprietary Information and Inventions Agreement; (ii) commission of any fraud against Isis or use or appropriation for personal use or benefit of any funds or properties of Isis not authorized by the Company to be so used or appropriated; (iii) conviction of a crime involving dishonesty or moral turpitude; (iv) conduct by you which in the good faith and reasonable determination of the Company demonstrates gross unfitness to serve in your then current capacity at Isis. In order to be eligible to receive the severance payments described herein, you will be required to execute an Employee Separation Agreement substantially in the form attached hereto as Exhibit A.

In the event that your employment is terminated by Isis as a result of a Change in Control (as defined herein), your severance payment shall be increased such that you receive a total of [number (#)] months of your then current base salary, less payroll deductions and withholdings. For purposes of this letter agreement, Change in Control will be defined as follows: (i) a sale of all or substantially all of the assets of Isis; (ii) a merger or consolidation in which Isis is not the surviving corporation and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which Isis is 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, and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by Isis or subsidiary of Isis or other entity controlled by Isis) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

Please keep in mind that this letter agreement is not intended to change your status as an at-will employee with Isis. As with all employees at Isis, you or Isis may terminate your employment at any time, for any reason whatsoever, with or without cause or advance notice subject to the provisions set forth herein.

If you have any questions or comments regarding the terms and conditions of this letter, please do not hesitate to contact me.

Very truly yours,

Isis Pharmaceuticals, Inc.

Patricia M. Lowenstam
Vice President, Human Resources

PML/jk

attachment

EXHIBIT A
SEPARATION AGREEMENT

This **SEPARATION AGREEMENT** ("Agreement") is made and entered into by and between ("Employee") and ("the Company") as of the ("Effective Date").

WHEREAS, the Company wishes to provide Employee with certain benefits in consideration of Employee's service to the Company and the promises and covenants of Employee as contained herein;

NOW, THEREFORE, in consideration of the mutual promises and covenants contained herein, it is hereby agreed by and between the parties hereto as follows:

1. **SEVERANCE PAYMENTS**. On ("Separation Date"), Employee shall cease to be an employee or officer of the Company for all purposes. In return for executing this Agreement, Employee will receive one (1) month of Employee's base salary in effect on the Separation Date, subject to standard payroll deductions and withholdings. In addition, if Employee has been continuously employed by the Company for a minimum of three (3) years, Employee will receive an additional two (2) weeks of base salary per year of service.

2. **ACCRUED SALARY AND PAID TIME OFF.** On or about the Separation Date, the Company will pay Employee all accrued salary, and all accrued and unused vacation, subject to standard payroll deductions and withholdings. Employee is entitled to these payments regardless of whether or not Employee signs this Agreement.

3. **EMPLOYMENT SEARCH SUPPORT**. Commencing on the Separation Date, the Company will provide Employee offsite employment search support through Right Management Associates as outlined in Exhibit A attached hereto.

4. **HEALTH INSURANCE.** To the extent permitted by law and by the Company's current group health insurance policies, after the Separation Date, Employee will be eligible to continue receiving health insurance benefits under the federal or state COBRA law at Employee's own expense and later to convert to an individual policy if desired. Employee will be provided with a separate notice regarding COBRA benefits. If Employee elects continued coverage under COBRA, the Company will reimburse Employee's COBRA premiums for one (1) month as part of this Agreement. In addition, to the extent permitted by law and by the Company's current vision and dental insurance policies, after the Separation Date, the Company will reimburse Employee's vision and dental benefit premiums for one (1) month.

5. **STOCK OPTIONS**. Pursuant to the Company's 199 Equity Incentive Plan (the "Plan") and Employee's Stock Option Agreement (a copy of which is attached hereto as Exhibit B), vesting of Employee's stock options will cease on the Separation Date. Employee's rights to exercise Employee's option as to any vested shares will be as set forth in the Plan and Employee's Stock Option Agreement.

6. **OTHER BENEFITS.** Except as expressly provided herein, Employee acknowledges that Employee will not receive (nor is entitled to receive) any additional compensation or benefits.

7. **RETURN OF COMPANY PROPERTY**. By three (3) days after the Separation Date, Employee will return to the Company all Company documents (and all copies thereof) and other Company property and materials in Employee's possession, or control, including, but not limited to, Company files, notes, memoranda, correspondence, lists, drawings, records, plans and forecasts, financial information, personnel information, customer and customer prospect information, sales and marketing information, product development and pricing information, specifications, computer-recorded information, tangible property, equipment, credit cards, entry cards, identification badges and keys; and any materials of any kind which contain or embody any proprietary or confidential information of the Company (and all reproductions thereof).

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8. **PROPRIETARY INFORMATION OBLIGATIONS**. Employee acknowledges that nothing herein shall impair the covenants and obligations set forth in Employee's Proprietary Information and Inventions Agreement, a copy of which is attached hereto as Exhibit C.

9. **EMPLOYEE'S RELEASE OF CLAIMS.** Except as otherwise set forth in this Agreement, in exchange for consideration under this Agreement to which Employee would not otherwise be entitled, Employee hereby releases, acquits and forever discharges the Company, its parents and subsidiaries, and their officers, directors, agents, servants, employees, attorneys, shareholders, successors, assigns and affiliates, of and from any and all claims, liabilities, demands, causes of action, costs, expenses, attorneys fees, damages, indemnities and obligations of every kind and nature, in law, equity, or otherwise, known and unknown, suspected and unsuspected, disclosed and undisclosed, arising out of or in any way related to agreements, events, acts or conduct at any time prior to and including the execution date of this Agreement, including but not limited to: all such claims and demands directly or indirectly arising out of or in any way connected with Employee's employment with the Company or the termination of that employment; claims or demands related to salary, bonuses, commissions, stock, stock options, or any other ownership interests in the Company, vacation pay, fringe benefits, expense reimbursements, severance pay, or any other form of compensation; claims pursuant to any federal, state or local law, statute, or cause of action including, but not limited to, the federal Civil Rights Act of 1964, as amended; the federal Americans with Disabilities Act of 1990; the federal Age Discrimination in Employment Act of 1967, as amended ("ADEA"); the California Fair Employment and Housing Act, as amended; tort law; contract law; wrongful discharge; discrimination; harassment; fraud; defamation; emotional distress; and breach of the implied covenant of good faith and fair dealing.

10. **SECTION 1542 WAIVER.** Employee acknowledges reading and understanding Section 1542 of the Civil Code of the State of California:

> **A general release does not extend to claims which the creditor does not know or suspect to exist in his favor at the time of executing the release, which if known by him must have materially affected his settlement with the debtor.**

Employee hereby expressly waives and relinquishes all rights and benefits under that section and any law or legal principle of similar effect in any jurisdiction with respect to the release of unknown and unsuspected claims granted in this Agreement.

11. **ARBITRATION**. To ensure rapid and economical resolution of any and all disputes that may arise in connection with the Agreement, the parties agree that any and all disputes, claims, causes of action, in law or equity, arising from or relating to this Agreement or its enforcement, performance, breach, or interpretation, with the sole exception of those disputes that may arise from Employee's Proprietary Information and Inventions Agreement, will be resolved by final and binding confidential arbitration held in San Diego, California and conducted by the American Arbitration Association ("AAA") under its then-existing Rules and Procedures. Nothing in this paragraph is intended to prevent either party from obtaining injunctive relief in court to prevent irreparable harm pending the conclusion of any such arbitration.

12. **ENTIRE AGREEMENT**. This Agreement, including all exhibits, constitutes the complete, final and exclusive embodiment of the entire agreement between Employee and the Company with regard to the subject matter hereof. It supersedes any and all agreements entered into by and between Employee and the Company where such other agreement may conflict with this agreement. It is entered into without reliance on any promise or representation, written or oral,

other than those expressly contained herein. It may not be modified except in a writing signed by Employee and a duly authorized officer of the Company. The parties have carefully read this Agreement, have been afforded the opportunity to be advised of its meaning and consequences by their respective attorneys, and signed the same of their own free will.

13. **MISCELLANEOUS**. This Agreement shall bind the heirs, personal representatives, successors, assigns, executors and administrators of each party, and inure to the benefit of each party, its heirs,

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successors and assigns. This Agreement shall be deemed to have been entered into and shall be construed and enforced in accordance with the laws of the State of California as applied to contracts made and to be performed entirely within California. If an arbitrator or court of competent jurisdiction determines that any term or provision of this Agreement is invalid or unenforceable, in whole or in part, then the remaining terms and provisions hereof shall be unimpaired, the invalid or unenforceable term or provision shall be modified or replaced so as to render it valid and enforceable in a manner which represents the parties' intention with respect to the invalid or unenforceable term or provision insofar as possible. This Agreement may be executed in two counterparts, each of which shall be deemed an original, all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the parties have duly authorized and caused this Agreement to be executed as follows:

EMPLOYEE

By:

EXHIBIT A
SEPARATION AGREEMENT

[Employee Over 40 Years Of Age—Exempt]

This **SEPARATION AGREEMENT** ("Agreement") is made and entered into by and between ("Employee") and ("the Company") as of the Effective Date of this Agreement, as defined in paragraph 10 below.

WHEREAS, the Company wishes to provide Employee with certain benefits in consideration of Employee's service to the Company and the promises and covenants of Employee as contained herein;

NOW, THEREFORE, in consideration of the mutual promises and covenants contained herein, it is hereby agreed by and between the parties hereto as follows:

1. **SEVERANCE PAYMENTS**. On ("Separation Date"), Employee shall cease to be an employee or officer of the Company for all purposes. In return for executing this Agreement, Employee will receive one (1) month of Employee's base salary in effect on the Separation Date, subject to standard payroll deductions and withholdings. In addition, if Employee has been continuously employed by the Company for a minimum of three (3) years, Employee will receive an additional two (2) weeks of base salary per year of service.

2. **ACCRUED SALARY AND PAID TIME OFF.** On or about the Separation Date, the Company will pay Employee all accrued salary, and all accrued and unused vacation, subject to standard payroll deductions and withholdings. Employee is entitled to these payments regardless of whether or not Employee signs this Agreement.

3. **EMPLOYMENT SEARCH SUPPORT**. Commencing on the Separation Date, the Company will provide Employee offsite employment search support through Right Management Associates as outlined in Exhibit A attached hereto.

4. **HEALTH INSURANCE.** To the extent permitted by law and by the Company's current group health insurance policies, after the Separation Date, Employee will be eligible to continue receiving health insurance benefits under the federal or state COBRA law at Employee's own expense and later to convert to an individual policy if desired. Employee will be provided with a separate notice regarding COBRA benefits. If Employee elects continued coverage under COBRA, the Company will reimburse Employee's COBRA premiums for one (1) month as part of this Agreement. In addition, to the extent permitted by law and by the Company's current vision and dental insurance policies, after the Separation Date, the Company will reimburse Employee's vision and dental benefit premiums for one (1) month.

5. **STOCK OPTIONS**. Pursuant to the Company's 199 Equity Incentive Plan (the "Plan") and Employee's Stock Option Agreement (a copy of which is attached hereto as Exhibit B), vesting of Employee's stock options will cease on the Separation Date. Employee's rights to exercise Employee's option as to any vested shares will be as set forth in the Plan and Employee's Stock Option Agreement.

6. **OTHER BENEFITS.** Except as expressly provided herein, Employee acknowledges that Employee will not receive (nor is entitled to receive) any additional compensation or benefits.

7. **RETURN OF COMPANY PROPERTY**. By three (3) days after the Separation Date, Employee will return to the Company all Company documents (and all copies thereof) and other Company property and materials in Employee's possession, or control, including, but not limited to, Company files, notes, memoranda, correspondence, lists, drawings, records, plans and forecasts, financial information, personnel information, customer and customer prospect information, sales and marketing information, product development and pricing information, specifications, computer-recorded information, tangible property, equipment, credit cards, entry cards, identification badges and keys; and any materials of any kind which contain or embody any proprietary or confidential information of the Company (and all reproductions thereof).

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8. **PROPRIETARY INFORMATION OBLIGATIONS**. Employee acknowledges that nothing herein shall impair the covenants and obligations set forth in Employee's Proprietary Information and Inventions Agreement, a copy of which is attached hereto as Exhibit C.

9. **EMPLOYEE'S RELEASE OF CLAIMS.** Except as otherwise set forth in this Agreement, in exchange for consideration under this Agreement to which Employee would not otherwise be entitled, Employee hereby releases, acquits and forever discharges the Company, its parents and subsidiaries, and their officers, directors, agents, servants, employees, attorneys, shareholders, successors, assigns and affiliates, of and from any and all claims, liabilities, demands, causes of action, costs, expenses, attorneys fees, damages, indemnities and obligations of every kind and nature, in law, equity, or otherwise, known and unknown, suspected and unsuspected, disclosed and undisclosed, arising out of or in any way related to agreements, events, acts or conduct at any time prior to and including the execution date of this Agreement, including but not limited to: all such claims and demands directly or indirectly arising out of or in any way connected with Employee's employment with the Company or the termination of that employment; claims or demands related to salary, bonuses, commissions, stock, stock options, or any other ownership interests in the Company, vacation pay, fringe benefits, expense reimbursements, severance pay, or any other form of compensation; claims pursuant to any federal, state or local law, statute, or cause of action including, but not limited to, the federal Civil Rights Act of 1964, as amended; the federal Americans with Disabilities Act of 1990; the federal Age Discrimination in Employment Act of 1967, as amended ("ADEA"); the California Fair Employment and Housing Act, as amended; tort law; contract law; wrongful discharge; discrimination; harassment; fraud; defamation; emotional distress; and breach of the implied covenant of good faith and fair dealing.

10. **ADEA WAIVER.** Employee acknowledges that Employee knowingly and voluntarily waives and releases any rights Employee may have under the ADEA, as amended. Employee also acknowledges that the consideration given for the waiver and release in the preceding paragraph hereof is in addition to anything of value to which Employee was already entitled. Employee further acknowledges that Employee has been advised by this writing, as required by the ADEA, that: (a) Employee's waiver and release do not apply to any rights or claims that may arise after the execution date of this Agreement; (b) Employee has the right to consult with an attorney prior to executing this Agreement; (c) Employee has forty-five (45) days to consider this Agreement (although Employee may choose to voluntarily execute this Agreement earlier); (d) Employee has seven (7) days following the execution of this Agreement by the parties to revoke the Agreement; and (e) this Agreement shall not be effective until the date upon which the revocation period has expired, which shall be the eighth day after this Agreement is executed by Employee, provided that the Company has also executed this Agreement by that date ("Effective Date").

11. **SECTION 1542 WAIVER.** Employee acknowledges reading and understanding Section 1542 of the Civil Code of the State of California:

> **A general release does not extend to claims which the creditor does not know or suspect to exist in his favor at the time of executing the release, which if known by him must have materially affected his settlement with the debtor.**

Employee hereby expressly waives and relinquishes all rights and benefits under that section and any law or legal principle of similar effect in any jurisdiction with respect to the release of unknown and unsuspected claims granted in this Agreement.

12. **ARBITRATION**. To ensure rapid and economical resolution of any and all disputes that may arise in connection with the Agreement, the parties agree that any and all disputes, claims, causes of action, in law or equity, arising from or relating to this Agreement or its enforcement, performance, breach, or interpretation, with the sole exception of those disputes that may arise from Employee's Proprietary Information and Inventions Agreement, will be resolved by final and binding confidential arbitration held in San Diego, California and conducted by the American Arbitration Association ("AAA") under its then-existing Rules and Procedures. Nothing in this paragraph is intended to prevent

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either party from obtaining injunctive relief in court to prevent irreparable harm pending the conclusion of any such arbitration.

13. **ENTIRE AGREEMENT**. This Agreement, including all exhibits, constitutes the complete, final and exclusive embodiment of the entire agreement between Employee and the Company with regard to the subject matter hereof. It supersedes any and all agreements entered into by and between Employee and the Company where such other agreement may conflict with this agreement. It is entered into without reliance on any promise or representation, written or oral, other than those expressly contained herein. It may not be modified except in a writing signed by Employee and a duly authorized officer of the Company. The parties have carefully read this Agreement, have been afforded the opportunity to be advised of its meaning and consequences by their respective attorneys, and signed the same of their own free will.

14. **MISCELLANEOUS**. This Agreement shall bind the heirs, personal representatives, successors, assigns, executors and administrators of each party, and inure to the benefit of each party, its heirs, successors and assigns. This Agreement shall be deemed to have been entered into and shall be construed and enforced in accordance with the laws of the State of California as applied to contracts made and to be performed entirely within California. If an arbitrator or court of competent jurisdiction determines that any term or provision of this Agreement is invalid or unenforceable, in whole or in part, then the remaining terms and provisions hereof shall be unimpaired, the invalid or unenforceable term or provision shall be modified or replaced so as to render it valid and enforceable in a manner which represents the parties' intention with respect to the invalid or unenforceable term or provision insofar as possible. This Agreement may be executed in two counterparts, each of which shall be deemed an original, all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the parties have duly authorized and caused this Agreement to be executed as follows:

EMPLOYEE

By:

Exhibit 10.4

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officers 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 officers 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: August 13, 2003

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

QuickLinks

Exhibit 31.1

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 quarterly report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officers 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 officers 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: August 13, 2003

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, Esq.
Chief Financial Officer

QuickLinks

Exhibit 31.2

CERTIFICATION

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Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 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 Quarterly Report on Form 10-Q for the period ended June 30, 2003, to which this Certification is attached as Exhibit 99.1 (the "Periodic 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 Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: August 13, 2003

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, Esq.
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.

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