UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

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

For the Quarterly Period Ended June 30, 2005

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 incorporation or organization)	(IRS Employer Identification No.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

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

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

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

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

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

The number of shares of voting common stock outstanding as of August 4, 2005 was 57,684,428.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Vitravene® is a registered trademark of Novartis AG.
Affinitak™ is a trademark of Eli Lilly and Company.

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	June 30, 2005 (Unaudited)	December 31, 2004 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 7,988	$ 27,250
Short-term investments	51,592	76,633
Contracts receivable	4,456	10,048
Inventory	1,071	2,722
Other current assets	7,260	8,956
Total current assets	72,367	125,609
Property, plant and equipment, net	22,837	28,454
Licenses, net	24,937	26,104
Patents, net	19,869	19,097
Deposits and other assets	3,220	3,854
Long-term investments	3,296	5,307
Total assets	$ 146,526	$ 208,425
LIABILITIES AND STOCKHOLDERS' DEFICIT		
Current liabilities:		
Accounts payable	$ 2,297	$ 6,967
Accrued compensation	1,736	3,475
Accrued liabilities	7,988	8,238
Current portion of long-term obligations	9,106	10,546
Current portion of deferred contract revenue	4,926	14,190
Total current liabilities	26,053	43,416
$5^1/_2$% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	119,432	111,611

Long-term deferred contract revenue, less current portion	230	531
Stockholders' deficit:		
Common stock, $0.001 par value; 100,000,000 shares authorized, 57,523,999 shares and 57,447,333 shares issued and outstanding at June 30, 2005 and December 31, 2004, respectively	58	57
Additional paid-in capital	623,385	623,706
Deferred compensation	(9)	(72)
Accumulated other comprehensive income	141	2,623
Accumulated deficit	(747,764)	(698,447)
Total stockholders' deficit	(124,189)	(72,133)
Total liabilities and stockholders' deficit	$ 146,526	$ 208,425

Note: The balance sheet at December 31, 2004 has been derived from the audited consolidated financial statements at that date.

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended June 30, 2005		Six Months Ended June 30, 2005	
	2005	2004	2005	2004
Revenue:				
Research and development revenue under collaborative agreements	$ 10,438	$ 8,217	$ 17,573	$ 15,215
Licensing and royalty revenue	154	1,626	461	6,931
Total revenue	10,592	9,843	18,034	22,146
Operating expenses:				
Research and development	20,950	32,036	43,311	60,983
General and administrative	1,910	2,568	4,048	5,021
Compensation expense (benefit) related to stock options	5	(3,421)	(628)	(183)
Restructuring activities	650	—	7,734	—
Total operating expenses	23,515	31,183	54,465	65,821
Loss from operations	(12,923)	(21,340)	(36,431)	(43,675)
Other income (expenses):				
Investment income	349	842	854	1,975
Interest expense	(7,085)	(5,451)	(13,740)	(10,555)
Net loss	(19,659)	(25,949)	(49,317)	(52,255)
Accretion of dividends on preferred stock	—	(180)	—	(361)
Net loss applicable to common stock	$ (19,659)	$ (26,129)	$ (49,317)	$ (52,616)
Basic and diluted net loss per share	$ (0.34)	$ (0.47)	$ (0.86)	$ (0.94)
Shares used in computing basic and diluted net loss per share	57,524	56,111	57,523	55,984

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Six Months Ended June 30,	
	2005	2004
Net cash used in operating activities	$ (41,392)	$ (54,885)
Investing activities:		
Purchase of short-term investments	(3,069)	(45,213)
Proceeds from the sale of short-term investments	28,188	108,747
Purchase of property, plant and equipment	(498)	(1,637)
Proceeds from the sale of property, plant and equipment	1,165	—

Other assets	(1,896)	(3,549)
Strategic investments	—	(10,000)
Net cash provided by investing activities	23,890	48,348
Financing activities:		
Net proceeds from issuance of equity	372	2,573
Proceeds from long-term borrowings	5,000	12,573
Principal payments on debt and capital lease obligations	(7,132)	(11,355)
Net cash provided by (used for) financing activities	(1,760)	3,791
Net increase (decrease) in cash and cash equivalents	(19,262)	(2,746)
Cash and cash equivalents at beginning of period	27,250	33,117
Cash and cash equivalents at end of period	$ 7,988	$ 30,371
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,502	$ 4,525
Supplemental disclosures of non-cash financing activities:		
Conversion of preferred stock into common stock	$ —	$ 14,934

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2005
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three and six month periods ended June 30, 2005 and 2004 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2004. The financial statements include all adjustments that Isis considers necessary for a fair presentation of the Company's 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, 2004 included in Isis' Annual Report on Form 10-K filed with the Securities and Exchange Commission.

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Hepasense, Ltd., and Orasense, Ltd.

2. Significant Accounting Policies

Revenue Recognition

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

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21 ("EITF 00-21") *Accounting for Revenue Arrangements with Multiple Deliverables*. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis records revenue from federal research grants during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products.

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

As part of Isis' alliance with Eli Lilly and Company ("Lilly"), in August 2001 Lilly provided Isis a $100.0 million interest free loan to fund the companies' joint research collaboration. As of June 30, 2005, Isis had drawn down the entire $100.0 million on this loan, which Isis converted into 2.5 million shares of its common stock in August 2005 according to its terms. Isis discounted the $100.0 million loan to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accreted 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 represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this value as deferred revenue and recognized it as revenue over the period of performance.

Licensing and royalty revenue

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

Concentration of Credit Risk

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

Cash, Cash Equivalents and Short-Term Investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income and these amounts have not been material. Isis determined that there were no other-than-temporary declines in value of its investments during the six months ended June 30, 2005 and 2004.

Valuation of Inventory

We include in inventory material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. During the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs.

Inventory includes the following categories as of June 30, 2005 and December 31, 2004 (net realizable value in thousands):

	June 30, 2005	December 31, 2004
Raw materials	$ 1,071	$ 1,329
Finished goods	—	1,393
Total Inventory	$ 1,071	$ 2,722

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 7 years and 15 years.

Patents

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

Fair Value of Financial Instruments

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

Long-Lived Assets

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. During the first half of 2005, Isis incurred a charge related to restructuring activities of $1.5 million primarily for the write-down of capitalized leasehold improvements in a building which Isis vacated during March 2005.

Use of Estimates

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

Long-Term Debt

Lilly provided to Isis a loan to fund its obligations under the multi-year strategic research collaboration the companies have participated in since August 2001, of which the entire $100.0 million was outstanding as of June 30, 2005. Under the terms of the loan agreement, Isis could repay this loan at the Company's option in either cash or its common stock at a fixed conversion price of $40 per share. In August 2005, Isis converted the loan into 2.5 million shares of Isis' common stock and extended the research collaboration. As part of the conversion and extension, Lilly agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestones and royalties in the event of a stock price decline.

Consolidation of Variable Interest Entities

Isis has implemented the provisions of Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of June 30, 2005, Isis had collaborative arrangements with two entities which it considers to be Variable Interest Entities ("VIE") under FIN 46.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible promissory note (the "Note"). Isis expensed the payments when made. The Note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1.0 million convertible promissory note (the "Note"). The Note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

Stock-Based Compensation

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program") to maintain one of Isis' key assets, its employee base, in a manner that was sensitive to shareholder interests. The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options, granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options vest over three years beginning on January 1, 2003 and expire on December 31, 2008. Isis accounts for the affected options using variable accounting consistent with the provisions of Accounting Principles Board ("APB")

Opinion No. 25 and FIN No. 44, and will continue to account for the affected options using variable accounting until all these options have been exercised or cancelled. As a result, Isis recorded compensation expense of $5,000 and compensation benefit of $628,000 during the three and six months ended June 30, 2005, respectively and compensation benefit of $3.4 million and $183,000 for the same periods in 2004.

Isis has adopted the disclosure-only provision of SFAS No. 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense for the Isis stock option plans, except for compensation expense primarily related to the affected options from the 2000 and 2003 option exchange programs. Had Isis determined compensation expense consistent with SFAS No. 123, Isis would have reported the following proforma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Net loss applicable to common stock—as reported	$ (19,659)	$ (26,129)	$ (49,317)	$ (52,616)
Net loss applicable to common stock—pro forma	$ (20,284)	$ (31,425)	$ (51,979)	$ (56,525)
Basic and diluted net loss per share—as reported	$ (0.34)	$ (0.47)	$ (0.86)	$ (0.94)
Basic and diluted net loss per share—pro forma	$ (0.35)	$ (0.56)	$ (0.90)	$ (1.01)

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

	June 30,	
	2005	2004
Risk-free interest rate	3.9%	4.6%
Dividend yield	0.0%	0.0%
Volatility	57.1%	67.8%
Expected Life	6.4 years	6.3 years

The weighted average fair values of options granted were $3.73 and $5.62 for the three and six months ended June 30, 2005, respectively and $6.94 and $6.92 for the three and six months ended June 30, 2004, respectively.

Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income*, requires Isis 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,	
	2005	2004	2005	2004
Comprehensive loss:				
Change in unrealized gains (losses)	$ (403)	$ (6,973)	$ (2,482)	$ (5,702)
Net loss applicable to common stock	(19,659)	(26,129)	(49,317)	(52,616)
Comprehensive loss	$ (20,062)	$ (33,102)	$ (51,799)	$ (58,318)

Included in comprehensive loss at June 30, 2004 was an unrealized loss of approximately $4.0 million related to Isis' equity investment in Alnylam Pharmaceuticals, Inc., which was part of a strategic alliance between the two companies.

Impact of Recently Issued Accounting Standards

On December 16, 2004, the Financial Accounting Standards Board ("FASB") issued SFAS 123(R), *Share-Based Payment* ("SFAS 123(R)"), which is a revision of SFAS 123. Generally, the approach in SFAS 123(R) is similar to the approach described in SFAS 123. However, SFAS 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values. Pro forma disclosure is no longer an alternative. This statement also eliminates the ability to account for share-based compensation transactions using APB Opinion No. 25. On April 14, 2005, the SEC deferred the effective date of SFAS 123(R). In accordance with the SEC's new effective date, Isis expects to adopt SFAS 123(R) on January 1, 2006.

SFAS 123(R) permits public companies to adopt its requirements using one of two methods: 1) A "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS 123 for all awards granted to employees prior to the effective date of SFAS 123(R) that remain unvested on the effective date; or 2) A "modified retrospective" method which includes the requirements of the modified prospective method described above, but also permits entities to restate based on the amounts previously recognized under SFAS 123 for purposes of pro forma disclosures either (a) all prior periods presented or (b) prior interim periods of the year of adoption. Isis has not yet determined what method it will use.

As permitted by SFAS 123, Isis currently accounts for share-based payments to employees using APB Opinion No. 25's intrinsic value method and, as such, generally recognizes no compensation cost for employee stock options. Accordingly, the adoption of SFAS 123(R)'s fair value method may have a significant impact on Isis' results of operations, although it will have no impact on its overall financial position. The impact of adoption of SFAS 123(R) cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had Isis adopted SFAS 123(R) in prior periods, the impact of that standard would have approximated the impact of SFAS 123 as described in the disclosure of pro forma net income and earnings per share in Note 1 to the condensed consolidated financial statements. SFAS 123(R) also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow as required under current literature. This requirement will reduce net operating cash flows and increase net financing cash flows in periods after adoption. While Isis cannot estimate what those amounts will be in the future, as a result of its accumulated losses to date, Isis has not recognized a benefit of tax deductions in excess of recognized compensation cost in operating cash flows.

In November 2004, the FASB issued SFAS No. 151, *Inventory Costs* ("SFAS 151"), an amendment of ARB No. 43, Chapter 4. This statement amends the guidance in ARB No. 43 Chapter 4, *Inventory Pricing*, to clarify the accounting for abnormal amounts of idle facility expense, freight, handling costs, and wasted material (spoilage). Paragraph 5 of ARB No. 43, Chapter 4, previously stated that " . . . under some circumstances, items such as idle facility expense, excessive spoilage, double freight, and rehandling costs may be so abnormal to require treatment as current period charges . . ." This statement requires that those items be recognized as current-period charges regardless of whether they meet the criterion of "so abnormal." In addition, this statement requires that allocation of fixed production overheads to the costs of conversion be based on the normal capacity of the production facilities. The provisions of this statement will be effective for inventory costs during the fiscal years beginning after June 15, 2005. Isis does not believe that the adoption of this statement will have a material impact on its financial condition or results of operations.

In March 2004, the FASB issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF 03-1, which was originally effective for interim and annual reporting periods beginning after June 15, 2004, requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. Isis does not expect that the adoption of EITF 03-1 will have a material impact on its operating results and financial position.

In May 2005, the FASB issued Statement of Financial Accounting Standards No. 154, "Accounting Changes and Error Corrections-a replacement of APB Opinion No. 20 and FASB Statement No. 3" ("SFAS 154"), which is effective for accounting changes and corrections of errors made in fiscal years beginning after December 15, 2005. SFAS 154 applies to all voluntary changes in accounting principles, and changes the accounting and reporting requirements for a change in accounting principle. SFAS 154 requires retrospective application to prior periods' financial statements of a voluntary change in accounting principle unless doing so is impracticable. APB 20 previously required that most voluntary changes in accounting principle be recognized by including in net income of the period in which the change occurred the cumulative effect of changing to the new accounting principle. SFAS 154 also requires that a change in depreciation, amortization, or depletion method for long-lived, non-financial assets be accounted for as a change in accounting estimate effected by a change in accounting principle. SFAS 154 carries forward without change the guidance in APB 20 for reporting the correction of an error in previously issued financial statements, a change in accounting estimate and a change in reporting entity, as well as the provisions of SFAS 3 that govern reporting accounting changes in interim financial statements. Isis is currently evaluating the impact of SFAS 154 on its consolidated financial statements, but does not expect that the impact will be material.

3. Strategic Alliances

Drug Discovery and Development

OncoGenex Technologies Inc

In January 2005, Isis broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drug candidates. In April 2005, OncoGenex selected its first drug candidate under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid Isis an up-front fee with a debt instrument, which, at OncoGenex's discretion is payable in cash or will convert into OncoGenex stock upon OncoGenex's completion of its next stock financing. OncoGenex will also pay Isis milestone payments totaling up to $5 million for key clinical and regulatory achievements, and royalties on future product sales of these drugs. Under the terms of the agreement, OncoGenex will be responsible for the preclinical and clinical development of the drug.

Sarissa, Inc.

In February 2005, Isis licensed one of its anti-cancer antisense drugs to Sarissa, a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a well-known drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs. Sarissa paid Isis a $1.0 million upfront fee with a debt instrument, which will convert into Sarissa stock upon Sarissa's completion of a financing. Isis has recognized a valuation allowance of $1.0 million to offset the debt instrument as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for key clinical and regulatory achievements and royalties on any product sales of this drug. Under the terms of the agreement, Sarissa will be solely responsible for preclinical and clinical development of the drug.

Pfizer, Inc

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second-generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis received a technology access fee of $1 million. In July 2005, Isis earned two milestone payments totaling $600,000 under the collaboration. Pfizer will also pay Isis additional milestone payments totaling up to $26.5 million for the first drug in the first major market for key research, clinical, regulatory and sales achievements and research funding. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration.

Eli Lilly and Company

In August 2005, Isis extended its multi-year strategic research collaboration with Lilly. Under the extension, Isis and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis scientists will be supported by collaboration funds, and Lilly scientists will be supported by Lilly. As part of the extension, the companies agree to add a second generation antisense inhibitor to Lilly's oncology drug discovery and development portfolio, Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis will be entitled to receive milestones of up to $28.0 million as this antisense inhibitor moves through various stages of development and royalties on any product sales of the drug. STAT-3 adds to the two other antisense oncology drugs in development at Lilly, one which is targeted to Survivin and one targeted to eIF-4E. The extended collaboration also provides Lilly access to Isis patents to support Lilly's internal antisense drug discovery program for a limited number of targets. In connection with the extension, Isis converted the interest-free $100.0 million loan that Lilly provided to Isis to fund its obligations under the research collaboration the companies have participated in since August 2001. Isis had the option of repaying the loan in cash or its common stock at a fixed conversion price of $40 per share. Given the favorable conversion terms, Isis chose to convert the loan into 2.5 million shares of the Company's common stock. The impact to the balance sheet will be reflected in the Company's financial results for the quarter ended September 30, 2005 as a reduction in long term debt and a decrease in stockholders' deficit. In connection with the extension and the conversion, Lilly agreed not to sell the conversion shares until at least the fourth quarter 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestone and royalties in the event of a stock price decline.

Ibis Division

In April 2005, Isis received two contracts totaling $1.5 million for the development of a new microbial forensics application for the TIGER biosensor system for use in the investigation of crimes involving infectious agents which compares the genetic "fingerprint" of an infectious agent to that of a potential source. The new awards will also support further enhancement of the Microbial Rosetta Stone (MRS) database to include additional genetic information on infectious agents. The MRS database is a key component of the TIGER biosensor system. These new contracts broaden TIGER's commercial applications and product opportunities for use by government and non-government customers.

In July 2005, Isis' Ibis division received contracts for $5.9 million from several government agencies to continue advancing the development of applications and to support the initial operations of the TIGER biosensor system. Funding was granted by several government agencies including the Defense Advanced Research Projects Agency (DARPA) and the Department of Homeland Security (DHS), under subcontracts from San Diego-based Science Applications International Corporation (SAIC).

In August 2005, Isis' Ibis division received a three-year grant worth up to $4.9 million from the National Institute of Allergies and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections using Ibis' TIGER biosensor system.

In August 2005, Isis' Ibis division shipped its first TIGER biosensor system to the United States Army Medical Research Institute for Infectious Disease, which will use the system to identify infectious agents for biowarfare defense.

4. Segment Information and Concentration of Business Risk

Segment Information

The following is information for revenue and loss from operations by segment.

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended June 30, 2005				
Revenue:				
Research and development	$ 7,541	$ 2,897	$ —	$ 10,438
Licensing and royalty	154	—	—	154
Total segment revenue	$ 7,695	$ 2,897	$ —	$ 10,592
Income (Loss) from operations	$ (11,873)	$ (395)	$ (655)	$ (12,923)
Three Months Ended June 30, 2004				
Revenue:				
Research and development	$ 4,254	$ 3,963	$ —	$ 8,217
Licensing and royalty	1,626	—	—	1,626
Total segment revenue	$ 5,880	$ 3,963	$ —	$ 9,843
Income (Loss) from operations	$ (24,450)	$ (311)	$ 3,421	$ (21,340)

	Drug Discovery and Development	Ibis	Corporate	Total
Six Months Ended June 30, 2005				
Revenue:				
Research and development	$ 12,351	$ 5,222	$ —	$ 17,573
Licensing and royalty	461	—	—	461
Total segment revenue	$ 12,812	$ 5,222	$ —	$ 18,034
Income (Loss) from operations	$ (27,818)	$ (1,507)	$ (7,106)	$ (36,431)
Six Months Ended June 30, 2004				
Revenue:				
Research and development	$ 8,455	$ 6,760	$ —	$ 15,215
Licensing and royalty	6,931	—	—	6,931
Total segment revenue	$ 15,386	$ 6,760	$ —	$ 22,146
Income (Loss) from operations	$ (42,389)	$ (1,469)	$ 183	$ (43,675)

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Partner A	44%	33%	50%	27%
Partner B	22%	0%	13%	2%
Partner C	14%	29%	13%	23%
Partner D	7%	12%	8%	7%
Partner E	0%	10%	0%	5%
Partner F	0%	5%	0%	25%

For the three and six months ended June 30, 2005, Isis derived approximately 27% and 30%, respectively, of its revenue directly and indirectly from agencies of the United States Government, including approximately 14% and 13% respectively, of revenue from one significant customer. For the three and six months ended June 30, 2004, Isis derived approximately 43% and 32%, respectively, of its revenue directly or indirectly from agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 41%, 17%, and 15% of contract receivables at June 30, 2005. Contract receivables from four significant partners comprised 30%, 20%, 17% and 10% of contract receivables at December 31, 2004.

5. Restructuring Activities

In connection with the decision to reorganize and refocus the Company's resources, in January 2005 Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of the Company's research and development laboratory in Singapore. In connection with the consolidation of its U.S. facilities, in June 2005 Isis completed the sale of its real property located at 2292 Faraday Avenue, Carlsbad, California to Shenco LLC. The real property included an approximately 18,848 square foot building, which Isis primarily used for office space. After repaying approximately $1.6 million of debt, which was secured by the property, and after deducting commissions and other expenses, Isis received net proceeds of approximately $957,000 for the sale of the property. Included in restructuring

activities in the second quarter of 2005 was a gain on the sale of this building of $1.3 million. In addition, Isis recently entered into a purchase and sale agreement for its manufacturing facility and a purchase and sale agreement for a building that Isis primarily used for laboratory space as further described in Item 5 of Part II of this report. Isis expects to substantially complete its restructuring efforts by the end of the third quarter 2005. Pursuant to SFAS No. 146, *"Accounting for Costs Associated with Exit or Disposal Activities,"* the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at June 30, 2005 (in thousands).

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at March 31, 2005	$ 1,302	$ 1,278	$ 990	$ 126	$ 3,696
Accrued and expensed	527	(22)	17	128	650
Charged against accrual	(422)	(1,001)	(30)	(178)	(1,631)
Balance at June 30, 2005	$ 1,407	$ 255	$ 977	$ 76	$ 2,715

6. Subsequent Events

In August 2005, Isis extended its multi-year strategic research collaboration with Lilly. Under the extension, Isis and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis scientists will be supported by collaboration funds, and Lilly scientists will be supported by Lilly. As part of the extension, the companies agree to add a second generation antisense inhibitor to Lilly's oncology drug discovery and development portfolio, Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis will be entitled to receive milestones of up to $28.0 million as this antisense inhibitor moves through various stages of development and royalties on any product sales of the drug. STAT-3 adds to the two other antisense oncology drugs in development at Lilly, one which is targeted to Survivin and one targeted to eIF-4E. The extended collaboration also provides Lilly access to Isis patents to support Lilly's internal antisense drug discovery program for a limited number of targets. In connection with the extension, Isis converted the interest-free $100.0 million loan that Lilly provided to Isis to fund its obligations under the research collaboration the companies have participated in since August 2001. Isis had the option of repaying the loan in cash or its common stock at a fixed conversion price of $40 per share. Given the favorable conversion terms, Isis chose to convert the loan into 2.5 million shares of the Company's common stock. The impact to the balance sheet will be reflected in the Company's financial results for the quarter ended September 30, 2005 as a reduction in long term debt and a decrease in stockholders' deficit. In connection with the extension and the conversion, Lilly agreed not to sell the conversion shares until at least the fourth quarter 2006, assuming the collaboration is not terminated earlier in exchange for certain credits against milestone and royalties in the event of a stock price decline.

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

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. 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, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems used to identify infectious organisms that are effective and commercially attractive and in the endeavor of building a business around such

products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. 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, 2004, 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 26 of this Report. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding 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 one marketed product and 11 antisense drugs, which we and our partners are advancing in pre-clinical and clinical development, the majority of which are in Phase I or Phase II human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, metabolic and cardiovascular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, including intravitreal, subcutaneous, topical cream, enema, aerosol, and oral formulations. In addition, our pipeline has matured to consist primarily of drugs based on our proprietary second-generation chemistry. Our second-generation antisense drugs offer a number of advantages over prior chemistries. Specifically, these drugs offer the potential for improved safety, increased potency and a longer half-life, which correlates with durability of therapeutic response and the potential for less frequent dosing. Physicians may be able to dose our second-generation drugs as infrequently as once every two weeks to once a month. We are also making progress on developing oral formulations of our second-generation antisense drugs. Recently, we expanded the clinical development program for our second-generation inhibitor of apoB-100 for the lowering of cholesterol, ISIS 301012, with the initiation of a Phase 1 study of an oral capsule formulation of ISIS 301012. Our oral formulations may increase the commercial value of our antisense drugs. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen), in 1998.

Our Ibis division has invented the TIGER biosensor system, a system that has the potential to revolutionize the identification of infectious diseases. We founded our Ibis division to take advantage of our expertise in RNA and utilize that knowledge and innovation to create a fundamentally different approach for the identification of bacterial and viral organisms. Our scientists have applied proprietary technologies to develop a biological sensor to identify

a broad range of infectious organisms contained in a sample, including those that are newly-emerging, genetically altered and unculturable. The division has successfully demonstrated proof-of-principle of the TIGER biosensor system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. In addition to bioweapons defense, Ibis has advanced the development of the TIGER biosensor system to include epidemiological surveillance, biological products screening and microbial forensics applications. These applications represent the first of many we plan to add to the TIGER biosensor system to enhance its commercial value and opportunity in the government, research, medical and diagnostic markets. Our Ibis division plans to commercialize the TIGER biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control, and infectious disease diagnostics.

To develop TIGER technology and applications, our Ibis division has received contracts from a number of government agencies, including the Defense Advanced Research Projects Agency (DARPA), the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Federal Bureau of Investigation (FBI), and the Department of Homeland Security (DHS). From inception through June 30, 2005, Ibis has earned $41.4 million in revenue from government partners. An additional $12.1 million is committed under existing contracts and grants, with the potential for added funding.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. To date, we have generated nearly $71 million from our intellectual property licensing program that helps support our internal drug discovery and clinical development programs.

The principal purpose of our intellectual property portfolio is to protect our products and those of our partners. Our intellectual property portfolio also enables us to expand our pipeline by granting other companies limited access to antisense technology through licenses we grant them. Licensing partnerships may include traditionally structured antisense drug discovery and development collaborations with large pharmaceutical companies like Lilly, Amgen, and most recently, Pfizer, Inc.

In May 2005, we entered into a multi-year drug discovery collaboration with Pfizer to identify second-generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, we received a $1.0 million technology access fee. Pfizer will also pay milestone payments for the first drug in the first major market for key research, clinical regulatory and sales achievements and research funding. To date, we have earned two milestone payments totaling $600,000 for our research within the collaboration. We will also receive royalties on the sale of drugs resulting from the collaboration.

In addition, we have extended our licensing partnerships to include our satellite company strategy in which we provide our expertise and intellectual property position in RNA-based therapeutics to industry partners that are interested in developing RNA-based therapeutics. We are able to pursue this partnering strategy because antisense allows us to produce more drug candidates than we can afford to develop on our own. We have implemented this integral component of our strategy through our partnerships with Alnylam Pharmaceuticals, Inc., Antisense Therapeutics, Ltd., Ercole, OncoGenex, Santaris Pharma A/S, and most recently, Sarissa.

Further, we have an active intellectual property licensing program in which we license aspects of our intellectual property to companies like Hybridon, Inc., Integrated DNA Technologies, Inc., Roche Molecular Systems, atugen A/S, Dharmacon, Inc. and Coley Pharmaceutical Group, Inc. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc. In December 2001, we licensed several chemistry patents to Eyetech for the development of Macugen, a drug for the treatment of wet age-related macular degeneration, or AMD, that Eyetech is co-developing and commercializing with Pfizer. In 2004, we earned $4.0 million in milestone payments from Eyetech associated with their filing of a New Drug Application for Macugen with the FDA and Eyetech's receipt of marketing clearance for the drug. In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA., Inc., in exchange for aggregate payments of $24 million over the next three years.

We are pursuing early-stage antisense mechanisms, including RNA interference, or RNAi, micro-RNA, and alternative splicing through research collaborations and partnerships, like our strategic alliances with Alnylam and Ercole.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. Our proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drug candidates for optimal use with particular targets and thus, to produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, over the past decade, our scientists have made great advances in chemistries, which we call our second-generation antisense drugs. Second-generation drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. We have also made significant progress in developing new formulations of antisense drugs, like oral, topical cream, subcutaneous, intravitreal, aerosol and enema that further expand the potential for antisense technology.

We and our partners currently have 11 drugs in development, of which four are in Phase II clinical development, four are in Phase I clinical development and three are in preclinical development. Our partners are developing, with our support, five of these 11 drugs, which substantially reduce our development costs.

Ibis Division. Within our Ibis division, we have invented a technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. TIGER is the product of core technology development and small molecule drug discovery research conducted within our Ibis division in its early years. Ibis' central focus now is to develop and commercialize our TIGER technology.

Recent Events

In December 2004, we made a strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. We announced this decision in January 2005. In the fourth quarter of 2004 we recorded a $32.4 million charge for restructuring activities resulting from this decision, which consisted of non-cash write-downs of tangible and intangible assets that were non-

essential to our current focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. We incurred additional charges relating to our restructuring activities of $7.7 million during the first half of 2005, including those associated with employee termination costs, termination of certain contractual obligations, the consolidation of our United States facilities, and the closure of our research and development laboratory in Singapore. In connection with the consolidation of our U.S. facilities, in June 2005 we completed the sale of an approximately 18,848 square foot building, which we primarily used for office space. After repaying approximately $1.6 million of debt, which was secured by the property, and after deducting commissions and other expenses, we received net proceeds of approximately $957,000 for the sale of the property. In addition, we recently entered into a purchase and sale agreement for our manufacturing facility, which we intend to leaseback as part of the sale. We also recently entered into a purchase and sale agreement for a building we primarily used for laboratory space. Additional information about the pending real estate transactions is included in Item 5 of Part II of this report.

Critical Accounting Policies

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

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determine appropriateness of the judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option and the expected stock price volatility over the term of the expected life.

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where we have billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

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

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. As of June 30, 2005, we had drawn down the entire $100.0 million on this loan. We are accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represents value Lilly gave to us to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance. In August 2005, in accordance with its terms, we converted this loan at $40 per share into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration. As part of the conversion and collaboration

extension, Lilly has agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestones and royalties in the event of a stock price decline.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestones upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated to future performance related to the achievement of the milestone. We recognized revenue during 2004 related to milestones achieved under our agreements with Eyetech, Lilly and Singapore EDB. Recently, we earned two milestone payments totaling $600,000 under our Pfizer collaboration, which we will recognize as revenue in our third quarter ending September 30, 2005.

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

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

Valuation of Investments in Marketable Securities

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

In addition to our investments in marketable securities, we also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

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

In December 2004, we made a strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. As a result, during the fourth quarter of 2004 we recorded charges of approximately $11.5 million related to the write-down of tangible and intangible assets, including equipment and patent costs that were non-essential to our current focus.

Valuation of Inventory

We include in inventory material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to our strategic decision to re-organize and re-focus our resources to advance our most promising second-generation drugs.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to

cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Assets

We recorded a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis division based on the segregation of revenue and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Proforma Stock-Based Compensation

We provide proforma net income and loss per share amounts in accordance with the disclosure only provision of Statement of Financial Accounting Standards No. 123, *"Accounting for Stock-Based Compensation."* or SFAS No. 123. The stock-based compensation expense used in these proforma amounts is based on the fair value of the option at the grant date, which uses the fair value pricing method described in SFAS No. 123. This method requires us to use several assumptions to estimate the fair value, including the expected life of the option and the expected stock price volatility over the term of the expected life. Should any of these assumptions change or differ from the actual life or actual stock price volatility, our pro forma results could differ substantially.

Effective in January 1, 2006, pursuant to the provisions of SFAS No. 123(R), *"Share-Based Payment,"* we will be required to recognize as a charge to our statement of operations the fair value of all share-based payments to employees, including stock option grants. We cannot currently predict the impact that this new accounting treatment will have on our statement of operations because it will depend on levels of share-based payments we grant in the future. However, accounting for share-based payments to employees using the fair value method will have no impact on our overall financial position.

Results of Operations

Total revenue for the three and six months ended June 30, 2005 was $10.6 million and $18.0 million, respectively, compared to $9.8 million and $22.1 million for the same periods in 2004. Our revenue fluctuates from period-to-period based on the nature and timing of license fees and milestones earned, and other deliverables under agreements with partners. Our ability to maintain revenue at current levels will depend on new revenue sources and the expansion of existing revenue sources for the remainder of 2005.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Drug Discovery and Development:				
Research and development revenue	$ 7,541	$ 4,254	$ 12,351	$ 8,455
Licensing and royalty revenue	154	1,626	461	6,931
	$ 7,695	$ 5,880	$ 12,812	$ 15,386
Ibis Division				
Research and development revenue	$ 2,897	3,963	5,222	6,760
Licensing and royalty revenue	—	—	—	—
	$ 2,897	$ 3,963	$ 5,222	$ 6,760
Total Revenue:				
Research and development revenue	$ 10,438	$ 8,217	$ 17,563	$ 15,215
Licensing and royalty revenue	154	1,626	461	6,931
	$ 10,592	$ 9,843	$ 18,034	$ 22,146

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the three and six months ended June 30, 2005 was $7.5 million and $12.4 million, respectively, compared to $4.3 million and $8.5 million for the same periods in 2004. The increase reflects revenue we earned from our partner OncoGenex in connection with clinical trial materials we sold to OncoGenex in the second quarter of 2005 and the expansion of our cancer collaboration with OncoGenex. The increase also reflects an increase in revenue related to additional drawdowns on our loan from Lilly. Our revenue from licensing activities and royalties for the three and six months ended June 30, 2005 was $154,000 and $461,000, respectively, compared to $1.6 million and $6.9 million for the same periods in 2004. We earned $5.5 million from Alnylam in the first half of 2004 in connection with our strategic alliance with Alnylam and a $1.0 million milestone from Eyetech for Macugen in the second quarter of 2004, which were the primary reasons for the decrease from 2004 to 2005.

Our Ibis division generates research and development revenue from grants and contracts from United States government agencies, including DARPA, CDC, FBI, DHS, and NIAID, a part of the NIH. Our Ibis division generated revenue of $2.9 million and $5.2 million for the three and six months ended June 30, 2005, respectively, compared to revenue of $4.0 million and $6.8 million for the same periods in 2004. Ibis' revenue may fluctuate on a quarter to quarter basis due primarily to the timing of equipment purchased in support of its government contracts. In general, when Ibis purchases equipment, it records expenses associated with the purchase and corresponding revenue. During 2004, Ibis was acquiring the necessary equipment components to build

the TIGER systems that Ibis expects to deploy to its government partners this year. As a result, the first half of 2004 included $2.8 million in revenue and associated expense related to these equipment purchases, compared to $656,000 for the same period in 2005. This variance in revenue related to equipment purchases was the primary reason for the decrease in revenue from the first half of 2004 to the first half of 2005.

We receive our DARPA funding through a subcontract with San Diego-based Science Applications International Corporation or SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 13% and 23% of our total revenue in the first half of 2005 and 2004, respectively, which represents 44% and 76% of our 2005 and 2004 Ibis division revenue, respectively. During 2004 and early 2005, we entered into several new government contracts, expanding our reach to multiple government agencies. Consequently, our government-funded revenues are subject to greater period-to-period fluctuations than in the past, depending on the timing of when we enter into and commence work under various contracts with these agencies.

From inception through June 30, 2005, Ibis has earned $41.4 million in revenue from various government agencies to further the development of our TIGER program. An additional $12.1 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. In addition, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

Total operating expenses for the three and six months ended June 30, 2005 were $23.5 million and $54.5 million, respectively, compared to $31.2 million and $65.8 million for the same periods in 2004. The change was primarily due to cost savings we achieved as a result of cost containment measures we implemented in the first quarter of 2005, which continued through the second quarter and, to a lesser extent, non-cash compensation benefit due to variable accounting for stock options. This decrease in operating expenses was offset in part by $7.7 million in charges we incurred during the first half of 2005 related to our restructuring activities. We expect these cost savings to continue through the remainder of 2005 as a result of our cost containment measures. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation related to stock options from operating expenses because it is based on the variability of our stock price rather than operations, and to exclude restructuring activities because the costs are directly related to isolated events.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis division, and R&D Support costs. As part of our corporate restructuring earlier this year, we consolidated our research manufacturing functions and our drug manufacturing functions into a combined manufacturing group that can serve the needs of both Antisense Research and Antisense Drug Development. We call this new function Manufacturing and Operations, and include the costs related to this new function in our research and development expenses. We expect that the consolidation will result in overall efficiencies and related cost savings. For the three and six months ended June 30, 2005, we incurred total research and development expenses of $21.0 million and $43.3 million, respectively, compared to $32.0 million and $61.0 million for the same periods in 2004. The $17.7 million decrease in operating expenses from the first half of 2004 to the same period in 2005 is attributed to cost savings achieved as a result of our restructuring activities. These cost savings include significant reductions in personnel costs, as well as a reduction in third party clinical development costs attributed to our decision to focus our research and development resources on our most promising second-generation drugs and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease.

Our research and development expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 17,916	$ 28,033	$ 37,132	$ 53,299
Ibis Division	3,034	4,003	6,179	7,684
Total research and development expenses	$ 20,950	$ 32,036	$ 43,311	$ 60,983

Antisense drug discovery costs for the three and six months ended June 30, 2005 were $4.8 million and $9.9 million, respectively, compared to $8.4 million and $16.7 million for the same periods in 2004. The decrease of $6.8 million from the first half of 2004 to the same period in 2005 was principally the result of cost savings achieved as a result of our first quarter restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Alicaforsen for Crohn's disease	$ 98	$ 1,546	$ 343	$ 3,002
Other antisense development products	5,108	7,011	10,689	13,319
Development overhead costs	1,838	3,782	3,689	6,329
Total antisense drug development	$ 7,044	$ 12,339	$ 14,721	$ 22,650

Antisense drug development expenditures were $7.0 million and $14.7 million for the three and six months ended June 30, 2005, respectively, compared to $12.3 million and $22.7 million for the same periods in 2004. The decrease of $8.0 million from the first half of 2004 to the same period in 2005, was primarily due to cost savings achieved as a result of our recent restructuring activities. These cost savings were primarily attributed to a decrease

in personnel costs and third party clinical development costs resulting from our decision to focus resources on our most promising second generation drug candidates. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. For example, during 2004, we decided not to initiate additional studies of ISIS 14803 and ISIS 104838. In addition we decided to discontinue further investment in the development of alicaforsen for Crohn's disease following disappointing results in Phase III trials for this drug. Generally, Phase III clinical trials are the longest, largest and most expensive component of the drug development process. Further, products in Phase III trials represent the most near term possibility of commercial success. In addition, because Phase III trials typically involve a well-defined protocol and require dedicated resources, it is easier for us to separately capture costs associated with these projects. Our Phase I and Phase II programs are really research programs that fuel our Phase III pipeline. When our products are in Phase I or Phase II clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase I" or "in Phase II," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product-to-product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. For example, during 2003, Lilly reimbursed us for our costs to develop Affinitak for the treatment of non small cell lung cancer. Our partners are developing, with our support, five of our 11 drug candidates, which substantially reduces our development costs.

We incurred development expenditures related to alicaforsen for Crohn's disease of $98,000 and $343,000 for the three and six months ended June 30, 2005, respectively, compared to $1.5 million and $3.0 million for the same periods in 2004. The decrease from the first half of 2004 to the same period in 2005 of $2.7 million was primarily due to the completion of our Phase III trials in December 2004. In December 2004, we reported the results of our Phase III clinical trials of alicaforsen in patients with Crohn's disease. In these trials alicaforsen did not demonstrate statistically significant induction of clinical remission compared to placebo. As a result of these data, we decided not to invest further in the development of alicaforsen for Crohn's disease.

We incurred expenses related to our other products in development of $5.1 million and $10.7 million for the three and six months ended June 30, 2005, respectively, compared to $7.0 million and $13.3 million for the same periods in 2004. The decrease of $2.6 million from the first half of 2004 to the same period in 2005, was primarily the result of a decrease in development activity related to our first-generation drugs, principally alicaforsen for ulcerative colitis. In December 2004, we announced the results of three Phase II studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen enema produced significant and long-lasting disease improvement. Costs for alicaforsen for ulcerative colitis have decreased in 2005 as compared to 2004 because we are using primarily internal resources as we prepare to meet with the FDA to discuss Phase III development plans for the drug. The decrease was offset in part by increased expenditures related to our most promising second-generation drug candidates, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the treatment of high cholesterol.

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. These costs for the three and six months ended June 30, 2005 were $1.8 million and $3.3 million, respectively. As discussed above, manufacturing and operations is a new function that was created in 2005 to provide manufacturing efficiencies and related cost savings. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements. We believe that it would be impractical to obtain comparative information for prior periods for this new function, and that such comparisons between any period in 2004 would be meaningless; therefore, we do not discuss these comparisons.

Our Ibis research and development expenses are the result of our performance under our contracts with DARPA, the FBI, the NIAID, a part of the NIH, the CDC and the DHS, in support of the ongoing development of our TIGER program. We include in the expenses for our Ibis division all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our TIGER

program. In addition, we allocate a portion of R&D Support costs and general and administrative costs to our Ibis division. Our Ibis division research and development expenses for the three and six months ended June 30, 2005 were $3.0 million and $6.2 million, respectively, compared to $4.0 million and $7.7 million for the same periods in 2004. During 2004, Ibis was acquiring the necessary equipment components to build the TIGER systems that Ibis expects to deploy to its government partners this year. As a result, the first half of 2004 included $2.8 million in expense related to these equipment purchases, compared to $656,000 for the same period in 2005. This was the primary reason for the decrease in Ibis' operating expenses from the first half of 2004 to the first half of 2005. We expect our costs for our Ibis division to increase as we continue to expand this business.

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D Support costs.

The following table sets forth information on R&D Support costs (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Personnel costs	$ 1,381	$ 2,771	$ 2,883	$ 5,432
Occupancy	1,642	1,443	3,718	3,109
Depreciation and amoritization	1,248	1,487	2,541	2,952
Insurance	295	297	594	569
Other	355	882	787	1,418
Total R&D Support costs	$ 4,921	$ 6,880	$ 10,523	$ 13,480

R&D Support costs for the three and six months ended June 30, 2005 were $4.9 million and $10.5 million, respectively, compared to $6.9 million and $13.5 million for the same periods in 2004. The decrease was primarily due to decreased personnel, facilities, equipment depreciation and patent amortization costs resulting from our restructuring activities, which included employee terminations, consolidation and closure of facilities, and the write-down of equipment and patents.

Our R&D Support costs by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 4,289	$ 6,213	$ 9,123	$ 12,089
Ibis Division	632	667	1,400	1,391
Total R&D Support costs	$ 4,921	$ 6,880	$ 10,523	$ 13,480

General and administrative expenses for the three and six months ended June 30, 2005 were $1.9 million and $4.0 million, respectively, compared to $2.6 million and $5.0 million for the same periods in 2004. The decrease was primarily related to a reduction in personnel and outside services costs resulting from our restructuring activities.

Our general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 1,653	$ 2,297	$ 3,498	$ 4,476
Ibis Division	258	271	550	545
Total general and administrative expenses	$ 1,911	$ 2,568	$ 4,048	$ 5,021

Total operating expenses included non-cash compensation expense related to stock options of $5,000 and a non-cash compensation benefit of $628,000 for the three and six months ended June 30, 2005, respectively, compared to a non-cash compensation benefit of $3.4 million and $183,000 for the same periods in 2004. The changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with Accounting Principles Board, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44.

During the first six months of 2005, we recorded $7.7 million in costs associated with our restructuring activities resulting from our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue our development of antisense technology. The 2005 charge for restructuring activities consists of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore. In connection with the consolidation of our facilities, in June 2005 we completed the sale of an approximately 18,848 square foot building, which we primarily used for office space. After repaying approximately $1.6 million of debt, which was secured by the property, and after deducting commissions, and other expenses, we received net proceeds of approximately $957,000 for the sale of the property. Included in restructuring activities in the second quarter of 2005 was a gain on the sale of this building of $1.3 million. In addition, we recently entered into a purchase and sale agreement for our manufacturing facility, which we intend to leaseback as part of the sale. We also recently entered into a purchase and sale agreement for another building we primarily used for laboratory space. We expect that our cost containment measures will continue to decrease our cash use in 2005 as compared to 2004.

Investment Income

Investment income for the three and six months ended June 30, 2005 totaled $349,000 and $854,000, respectively, compared to $842,000 and $2.0 million for the same periods in 2004. The decrease in investment income for the first six months of 2005 as compared to the same period in 2004 was primarily due to our lower average cash and investments balances for the first six months of 2005 compared to the first six months of 2004.

Interest Expense

Interest expense for the three and six months ended June 30, 2005 totaled $7.1 million and $13.7 million, respectively, compared to $5.5 million and $10.6 million for the same periods in 2004. This increase was due to the effect of a higher debt balance during 2005 than during 2004 related to an increase in the loan to fund our Lilly research collaboration offset in part by a decrease in the carrying value of our term loan from Silicon Valley Bank.

Net Loss Applicable to Common Stock

For the three and six months ended June 30, 2005, we reported a net loss applicable to common stock of $19.7 million and $49.3 million, respectively, compared to a net loss applicable to common stock of $26.1 million and $52.6 million for the same periods in 2004. Our net loss applicable to common stock for the first six months of 2004 included $361,000 of accreted dividends on preferred stock. The decrease in net loss applicable to common stock for the six months ended June 30, 2005 compared to the same period in 2004 was primarily the result of a decrease in operating expenses as a result of cost savings achieved by our restructuring activities. Offsetting, in part, the decrease in operating expenses was $7.7 million in costs related to restructuring activities, an increase in interest expense due to the effect of a higher debt balance in 2005 as compared to 2004, and a decrease in investment income due to our lower average cash and investments balance in 2005 as compared to 2004.

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, 2005, we have earned approximately $461.1 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 $593.6 million from the sale of equity securities. We have borrowed approximately $387.1 million under long-term debt arrangements to finance a portion of our operations.

At June 30, 2005, we had cash, cash equivalents and short-term investments of $59.6 million, working capital of $46.3 million and a stockholders' deficit of $124.2 million. In comparison, we had cash, cash equivalents and short-term investments of $103.9 million, working capital of $82.2 million and a stockholders' deficit of $72.1 million as of December 31, 2004. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, pursue patents, and to pay our debt and capital lease obligations.

As of June 30, 2005, our debt and other obligations totaled $256.8 million, compared to $258.9 million at December 31, 2004. Our debt and other obligations at June 30, 2005 included current deferred contract revenue related to our Lilly loan of approximately $3.3 million and other contractual obligations. The decrease in our debt and other obligations was primarily due to the declining balance on our Silicon Valley Bank term loan offset, in part, by 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 amounts at 20% and accreting to their face value over their term by recording interest expense.

We will continue to use lease financing as long as the terms remain commercially attractive. Consistent with this, in July 2005 we entered into a $3.0 million equipment lease line with General Electric Capital Corporation. The lease line is effective for purchases through May 2006 and carries an interest rate of the three year treasury rate plus 1.06% at the time of drawdown. This leaseline will be secured by any equipment purchased under the line. To date, we have not drawn any funds under this leaseline.

Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least mid 2007. The following table summarizes our contractual obligations as of June 30, 2005. 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 millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Lilly Research Collaboration Loan	$ 100.0	$ 100.0	$ —	$ —	$ —
$5^1/_2$% Convertible Subordinated Notes	125.0	—	—	125.0	—
Standard Operating Debt	27.4	6.5	17.3	3.6	—
Capital Lease and Other Obligations	4.3	2.6	1.7	—	—
Operating Leases	8.7	2.7	4.0	1.8	0.2

Our contractual obligations consist primarily of our publicly traded convertible debt and Lilly research collaboration loan, which we converted in August 2005 into 2.5 million shares of our common stock. Under the terms of the loan, we could repay the loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. Given the favorable conversion terms, we chose to convert the loan. Under the terms of the conversion and Lilly collaboration extension, Lilly agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration doesn't terminate earlier, in exchange for certain credits against milestone and royalties in the event of a stock price decline. Because the loan was repayable in cash or stock at our option, we classified it as a long-term obligation at June 30, 2005. As of June 30, 2005, the balance in long-term obligations was $96.7 million and the balance in deferred revenue was $3.3 million. The impact to the balance sheet of the loan conversion will be reflected in our financial results for the quarter ended September 30, 2005 as a reduction in long term debt and a decrease in shareholders' deficit. In addition, we also have standard operating debt, capital leases and other obligations. Our standard operating debt includes a term loan from Silicon Valley Bank, and our mortgage loan payable to another bank. In June 2005, we repaid $1.6 million of our mortgage loan payable when we completed the sale of a piece of our real property that secured the mortgage.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At June 30, 2005, the principal outstanding on the notes was $125.0 million.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 6.0% at June 30, 2005. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at June 30, 2005 was $23.2 million.

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2005 for the purchase of services and materials as part of our normal course of business.

We plan to continue to enter into more collaborations with partners to provide for additional revenue and cash to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this report on 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.

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

Because drug discovery and development 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, 2005, we had accumulated losses of approximately $747.8 million and a stockholders' deficit of approximately $124.2 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 have only one product, Vitravene, approved for commercial use. 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 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 United States Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

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

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease; the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. 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 that have not met the primary clinical end points in their initial Phase III studies.

In March 2003, we reported the results of a Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase III clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. In December 2004, we reported the results of our Phase III clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

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

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

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

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

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

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.

To date, 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.

We have entered into collaborative arrangements with third parties to develop many of our 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 fails 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. For example, in November 2004 based on the outcome of both Phase III trials, Lilly discontinued its investment in Affinitak.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis division and the development of our TIGER system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical company or government partners stopped funding and/or developing these products, our

business could suffer and we may not have the resources available to develop these products on our own.

Certain of our partners are pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of a drug candidate.

In addition, the disappointing results of the two Affinitak trials, our Phase III clinical trials of alicaforsen in patients with active Crohn's disease or any future clinical trial failures could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

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

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

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

All of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least mid 2007. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will 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 our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our TIGER system to identify infectious organisms; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, product candidates or products.

If we cannot manufacture our products or contract with a third party to manufacture our products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial

manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

If we fail to compete effectively, our products will not contribute significant revenues.

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

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

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

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

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 arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. 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, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

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

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

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

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

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2005, the market price of our common stock has ranged from $2.76 to $6.67 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights to Eli Lilly and Company which cover approximately 2.5 million shares of our common stock we issued to Lilly upon the conversion of outstanding convertible securities. The addition of these shares into the market, may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on, and our Registered Independent Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board, or PCAOB, or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT 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

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our

disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2005. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2005.

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

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

PART II – OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Ajinomoto Co, Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto, filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, which purports to license certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the '830 patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. Ajinomoto also seeks a determination that the license is still in force. We have not yet filed an answer, and a hearing has not yet been set. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position in arbitration.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

On August 5, 2005, we issued 2.5 million shares of our common stock to Lilly in conjunction with the conversion of our $100.0 million loan from Lilly.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

On May 26, 2005, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect three directors to serve as Class II directors of the Company and one director to serve as a Class I director for the Company. For Director number one, Spencer R. Berthelsen, the number of votes for and withheld was 51,713,990 and 733,922, respectively. For Director number two, Joseph H. Wender, the number of votes for and withheld was 50,369,821 and 2,078,091, respectively. For Director number three, B. Lynne Parshall, the number of votes for and withheld was 51,041,581 and 1,406,331, respectively. For Director number four, Richard D. DiMarchi, the number of votes for and withheld was 51,675,710 and 772,202, respectively.

(2) To ratify the appointment of Ernst & Young LLP as the Company's independent registered public accounting firm for the fiscal year ending December 31, 2005. The number of votes for, against and abstaining was 51,295,369; 1,041,135 and 111,407, respectively.

ITEM 5. OTHER INFORMATION

a. On June 28, 2005, we entered into an agreement, pursuant to which we have agreed to sell our real property located at 2280 Faraday Avenue, Carlsbad, California to Electro Surface Technology, Inc. ("EST") for a purchase price of $3,200,000 (the "2280 Sale"). The real property included an approximately 25,603 square foot building which we primarily used for laboratory and office space. We expect to repay approximately $2.0 million of debt which is secured by the property.

The 2280 Sale is scheduled to close in September 2005. EST has until September 1, 2005 to inspect the property and may terminate the 2280 Sale, in its sole discretion and for any reason prior to the expiration of the inspection period. After the inspection period, but prior to the closing of the 2280 Sale, EST may terminate the 2280 Sale by forfeiting its deposit on the property, except that EST may terminate the 2280 Sale prior to the closing without forfeiting the deposit if:

- EST cannot obtain sufficient title insurance on the property; or
- We fail to perform our obligations under the 2280 Purchase Agreement or if the representations and warranties made by us are inaccurate;

We are selling the property as part of our ongoing restructuring efforts, and we estimate the restructuring gain associated with the sale of the property will be approximately $1.1 million.

b. On July 21, 2005, we entered into an agreement, pursuant to which we have agreed to sell our real property located at 2282 Faraday Avenue, Carlsbad, California to BioMed Realty, L.P. ("BioMed") for a purchase price of $8,500,000 (the "2282 Sale"). The real property includes an approximately 28,704 square foot building which we primarily use for manufacturing. As part of the 2282 Sale, we will lease back

the property from BioMed for an initial term of 15 years with an initial rent of $2.60 per rentable square foot. We expect to repay approximately $2.3 million of debt which is secured by the property.

The 2282 Sale is scheduled to close in September 2005. BioMed has until September 6, 2005 to inspect the property and may terminate the 2282 Sale, in its sole discretion and for any reason prior to the expiration of

the inspection period. After the inspection period, but prior to the closing of the 2282 Sale, BioMed may terminate the 2282 Sale by forfeiting its deposit on the property, except that BioMed may terminate the 2282 Sale prior to the closing without forfeiting the deposit if:

- BioMed cannot obtain sufficient title insurance on the property;
- We fail to perform our obligations under the 2282 Purchase Agreement or if the representations and warranties made by us are inaccurate;
- the physical condition of the property changes before the closing date, reasonable wear and tear excluded;
- We are the subject of a proceeding under the federal bankruptcy laws or any state law for relief of debtors;
- Our financial condition substantially changes before the closing date, adjusting for our historical cash burn rate; or
- If a moratorium, statute or regulation of any governmental agency or order or ruling of any court is enacted or issued which would materially adversely affect the value or operation of the property.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Collaborative Research Agreement dated May 24, 2005 between Isis Pharmaceuticals, Inc. and Pfizer Inc (with certain confidential information deleted).
10.2	Agreement for Purchase and Sale of 2280 Faraday Ave, Carlsbad, CA, dated June 28, 2005.
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.

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 Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 9, 2005
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 9, 2005

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

COLLABORATIVE RESEARCH AGREEMENT

This **COLLABORATIVE RESEARCH AGREEMENT** ("Agreement") is entered into as of May 24, 2005 by and between **PFIZER INC**, a Delaware corporation, having an office at 235 East 42nd Street, New York, New York 10017 and its Affiliates ("Pfizer"), and **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having an office at 1896 Rutherford Road, Carlsbad, CA 92008 ("Isis").

WHEREAS, Isis has expertise in the discovery, research, and development of antisense oligonucleotides; and

WHEREAS, Isis has discovered and developed proprietary antisense 2'- MOE chemistry, methods of use, design motifs and mechanism technology; and

WHEREAS, the parties plan to seek patent protection for all Products which make up the subject matter of this Agreement and the License Agreement; and

WHEREAS, Pfizer has the capability to undertake research for the discovery and evaluation of agents for treatment of disease and also the capability for clinical analysis, manufacturing and marketing of such agents; and

WHEREAS, Pfizer and Isis enter into this Agreement to discover and develop therapeutic antisense oligonucleotide agents;

NOW, THEREFORE, the parties agree as follows:

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1. **Definitions**.

The capitalized terms used in this Agreement, and not defined elsewhere in it, shall have the meanings specified for such terms in Exhibit A.

2. **Collaborative Research Program**.

2.1 **Purpose.** Isis and Pfizer shall conduct the Research Program throughout the Contract Period. The objective of the Research Program is to discover and develop Products.

2.2 **Research Plan**. The Research Plan for the first Commitment Year is described in the attached Exhibit I. For each Commitment Year after the first, the Research Plan shall be prepared by the Research Committee for submission to and approval by Pfizer and Isis no later than ninety (90) days before the end of the prior Commitment Year. Each Research Plan for each succeeding Commitment Year shall be appended to Exhibit I and made part of this Agreement.

2.3 **Exclusive Collaboration Gene Targets**. Isis agrees, subject to Section 10.1 of this Agreement and Section 11.1 of the License Agreement, that neither Isis nor any Isis controlled entities shall conduct research itself or sponsor any other research in the Area, or engage in any research sponsored by any third party in the Area, without Pfizer's prior written consent.

2.4 **Substitution of [***].** If the Research Committee determines that **[***]**, Pfizer, at its election, may substitute **[***]**, to be mutually agreed upon by the parties, for **[***]**. Upon substitution, the new **[***]** shall be deemed **[***]** and the removed **[***]** shall no longer be deemed **[***]**. The removed **[***]** will be subject to Sections 10 and 11 of this Agreement. Pfizer shall provide Isis with written notice of the substituted **[***]** within sixty (60) days of the Research Committee decision. Subject to the foregoing, Pfizer will have the right to make only **[***]** and at no time will there be more than **[***]** (**[***]**) Exclusive Collaboration Gene Targets.

Isis must accept such substituted **[***]** within **[***]** (**[***]**)**[***]** of receipt of such written notice by Pfizer, unless:

(a) such substituted **[***]** (or any ASO directed thereto) is subject to a written agreement between Isis and a third party made prior to Isis' receipt of such written notice which precludes Isis from agreeing as set out in Section 2.3 or, **[***]**;

(b) it is, at the time of receipt of such written notice, conducting or planning to conduct an internal product discovery or development program relating to such substituted **[***]**, independent of the Research Program, as can be demonstrated by Isis' written records.

2.5 **[***].** The parties agree to conduct research on **[***]** as **[***]**, pursuant to the Research Plan. The parties agree to conduct research on **[***]**on a non-exclusive basis. For the avoidance of doubt, Isis and Pfizer shall have the right to collaborate with other parties and conduct internal research on the **[***]**without limitation.

2.6 **[***]**. [***]**, and has filed a patent application claiming **[***]**. So long as **[***]**, under Section 5.2(a) Pfizer has the right to make and use **[***]**, and pursuant to Section 5.3, Pfizer has the right to have the **[***]**Patent Rights assigned to it.

2.7 **Research Committee**.

2.7.1 **Purpose**. Pfizer and Isis shall establish a Research Committee (the "Research Committee"):

(a) to review and evaluate progress under the Research Plan;

(b) to prepare the Research Plan for each Commitment Year other than for the first Commitment Year; and

(c) to coordinate and monitor publication of research results obtained from and the exchange of information and materials that relate to the Research Program.

2.7.2 **Membership**. Pfizer and Isis each shall appoint, in its sole discretion, three members to the Research Committee. Substitutes may be appointed at any time.

The members initially shall be:

Pfizer Appointees:

[***]

[***]

[***]

Isis Appointees:

[***]

[***]

[***]

2.7.3 **Chair**. The Research Committee shall be chaired by two co-chairpersons, one appointed by Pfizer and the other appointed by Isis.

2.7.4 **Meetings**. The Research Committee shall meet at least quarterly, at places and on dates selected by each party in turn. Representatives of Pfizer or Isis or both, in addition to members of the Research Committee, may attend such meetings at the invitation of either party.

2.7.5 **Minutes**. The Research Committee shall keep accurate minutes of its deliberations which record all proposed decisions and all actions recommended or taken. Drafts of the minutes shall be delivered to all Research Committee members within ten (10) business days after each meeting. The party hosting the meeting shall be responsible for the preparation and circulation of the draft minutes. Draft minutes shall be edited by the co-chairpersons and shall be issued in final form only with their approval and agreement.

2.7.6 **Decisions**. All technical decisions of the Research Committee shall be made by unanimous vote of the members present (so long as at least one Isis-appointed member and one Pfizer-appointed member are present). If a dispute, controversy or difference between the parties arises over technical issues (in each case, a "Dispute"), then such Dispute first shall be referred to the Research Committee to seek resolution of the Dispute. In such an event, the Research Committee shall hold at least one (1) meeting within thirty (30) days of the date on which the Dispute is referred to the Research Committee by any member thereof. In the event that the Research Committee is unable to resolve the Dispute within forty-five (45) days of the date on which the Dispute is referred to the Research Committee, each party shall designate a member of its senior management (not on the Research Committee) to discuss the Dispute in an effort to settle it amicably during a period of no less than thirty (30) days. Subject to Section 2.6.1 of the License Agreement, Pfizer shall have all decision making authority regarding the research, development and commercialization of Products. However, under no circumstances shall Isis be required to perform work outside the scope of the Research Plan or incur costs beyond those provided for in this Agreement or the Research Plan.

2.7.7 **Expenses**. Pfizer and Isis shall each bear all expenses of their respective members related to their participation on the Research Committee.

2.8 **Reports and Materials**.

2.8.1 **Reports**. During the Contract Period, Pfizer and Isis each shall furnish to the Research Committee:

(a) summary written reports within **[***]** (**[***]**) days after the end of each three-month period commencing on the Effective Date, describing its progress under the Research Plan; and

(b) detailed written reports within **[***]** (**[***]**) days after the end of each Commitment Year, describing the work accomplished by it under the Research Plan during the Commitment Year and discussing and evaluating the results of such work; and

(c) detailed written reports within **[***]** (**[***]**) days upon the completion of each research activity eligible for a milestone payment, describing the work accomplished in the completion of each milestone.

2.8.2 **Materials**. Isis and Pfizer shall, during the Contract Period, as a matter of course as described in the Research Plan, or upon each other's written or oral request, furnish to each other samples of biochemical, biological or synthetic chemical materials which are part of **[***]**, Isis Technology, Isis Know-how, Isis Licensed Technology, **[***]**, Program Technology or Program Know-how and which are necessary for each party to carry out its responsibilities under the Research Plan. Isis shall, upon request, deliver to Pfizer samples of any material made pursuant to and during activities described in the Research Plan. To the extent that the quantities of materials requested by either party exceed the quantities set forth in the Research Plan, the requesting party shall reimburse the other party for the reasonable costs of such materials if they are furnished.

2.8.3 **Restrictions on Transferring Materials**. Pfizer and Isis recognize that the biological, synthetic chemical and biochemical materials which are part of **[***]**, Isis Technology, Isis Know-how, **[***]**, Isis Licensed Technology, Program Technology, or Program Know-how represent commercial assets. Therefore, throughout the Contract Period and for **[***]** thereafter, Isis and Pfizer agree not to transfer materials of the other party to any third party except for agents, unless prior written consent for any such transfer is obtained from the other party. Isis and Pfizer each represent that any employees, Affiliates, agents and any consultants to whom materials of the other party are transferred are bound by agreement to use such materials only as expressly permitted by this Agreement, and by assignment obligations in favor of the transferring party as are appropriate to effect the ownership provisions of Section 5.1.

2.9 **Laboratory Facility and Personnel**. Isis shall provide suitable laboratory facilities, equipment and personnel for the work to be done by Isis in carrying out the Research Program.

2.10 **Diligent Efforts**. Pfizer shall use Commercially Reasonable Efforts and Isis shall use commercially reasonably efforts to achieve the objectives of the Research Program and Research Plan.

3. Funding.

3.1 **Technology Access Fee**. In consideration of disclosure to Pfizer of Isis' proprietary 2'-MOE chemistry and Isis' related technical knowledge and expertise, Pfizer shall pay to Isis a one-time, non-refundable, non-creditable technology access fee of one million dollars ($1,000,000) upon execution of this Agreement.

3.2 **Research Funding.**

3.2.1 Pfizer shall fund the research to be performed by Isis, pursuant to the Research Plan, by making payments upon initiation of the following activities:

(a) **[***]**: **$[***]**

(b) **[***]**: **$[***]**

(c) **[***]**: **$[***]**

(d) **[***]**: **$[***]**

3.2.2 Pfizer may further elect to fund certain research activities to be performed by Isis, pursuant to the Research Plan, by providing written notice to Isis at least **[***]** (**[***]**) days in advance of the desired initiation of the research. Pfizer shall fund the elected research upon initiation of the following activities:

(a) **[***]**: **$[***]**

(b) **[***]**: **$[***]**

(c) **[***]**: **$[***]**

3.2.3 Pfizer may elect to fund research activities to be performed by Isis pursuant to the Research Plan in addition to those designated in Sections 3.2.1 and 3.2.2. Upon request of the Research Committee, Isis shall submit to Pfizer a written quotation of the work to be performed, based upon Isis' reasonable costs. Pfizer may elect to fund such research activity

by providing written notice to Isis at least **[***]** (**[***]**) days in advance of the desired initiation of the research.

3.2.4 Pfizer may elect to purchase from Isis a supply of ASOs for the conduct of preclinical studies at a price, per single order, of (a) for the first gram (or fraction thereof), **[***]** dollars ($**[***]**) and (b) for each additional gram, **[***]** dollars ($**[***]**) provided that, for each additional gram, the price will be pro-rated for amounts less than an entire gram. Pfizer shall provide written notice to Isis of its election to purchase a specified quantity of ASOs.

3.3 **Research Milestone Payments.** Pfizer shall make research milestone payments to Isis upon achievement of certain events as described in the Research Plan, according to the following schedule:

(a) **[***]**: **$[***]**

(b) **[***]**: **$[***]**

(c) **[***]**: **$[***]**

(d) **[***]**: **$[***]**

(e) Notwithstanding any determination that any milestone in Sections 3.3(a)-(c) have not been successfully met for an ASO against an Exclusive Collaboration Gene Target, if **[***]**, then **[***]** shall **[***]**.

For any milestones achieved by Pfizer, within **[***]** days of such achievement Pfizer will provide Isis written notice of such achievement.

3.4 **Research Payments for [***] Substitution.** In the event that Pfizer elects to substitute **[***]** pursuant to Section 2.4, Pfizer shall pay Isis (a) **[***]**,**[***]**dollars ($**[***]**) and (b) **[***]**,**[***]**dollars ($**[***]**).

3.5 **US Funds**. Each payment pursuant to this Agreement shall be paid by Pfizer in U.S. currency by wire transfer in immediately available funds to an account designated by Isis, or by other mutually acceptable means within **[***]** (**[***]**) days after receipt and acceptance by Pfizer of the invoice from Isis.

3.6 **Records**. Isis will maintain all data and information that relate to supporting Pfizer's intellectual property position (including the disks and/or tapes upon which such data is stored, and laboratory notebooks, documents, reports and other material(s) prepared by Isis or its

agents) in confidential storage for a period of **[***]** (**[***]**) years following the earlier of the expiration or termination of this Agreement.

4. Treatment of Confidential Information.

4.1 **Confidentiality**.

(a) Subject to permitted disclosure under Sections 4.1(c) and 4.5 and the obligations set forth in Section 4.3 and the publication rights set forth in Section 4.2, Pfizer and Isis each agree that, during the term of this Agreement and for **[***]** thereafter, it will keep confidential all Isis Confidential Information or Pfizer Confidential Information, as the case may be, that is disclosed to it, or to any of its Affiliates, pursuant to this Agreement. Subject to Section 11, Program Technology and Program Know-how shall be deemed Pfizer Confidential Information.

(b) Neither Pfizer nor Isis shall use the other's Confidential Information except as expressly permitted in this Agreement.

(c) Pfizer and Isis each agree that any disclosure of the other's Confidential Information to any of its officers, employees, agents or Affiliates shall be made only if and to the extent necessary to carry out its responsibilities under this Agreement and shall be limited to the maximum extent possible consistent with such responsibilities. Pfizer and Isis each agree not to disclose the other's Confidential Information to any individual entity or party for whom disclosure is not expressly permitted under this Section under any circumstance without written permission from the other party. Each party shall take such action to preserve the confidentiality of each other's Confidential Information as it would customarily take to preserve the confidentiality of its own Confidential Information. Each party, upon the other's request, will return all the Confidential Information disclosed to the other party pursuant to this Agreement, including all copies and extracts of documents, within sixty (60) days of the request upon the termination of this Agreement except for one (1) copy which may be kept for the purpose of complying with continuing obligations under this Agreement.

(d) Isis and Pfizer each represent that all of its employees, Affiliates, agents, and any consultants to such party, who shall have access to **[***]**, Isis Technology, Isis Know-how, Isis Manufacturing Technology, Isis Manufacturing Know-how, **[***]**, Isis Licensed Technology, Program Technology, Program Know-how, Pfizer Confidential Information or Isis

Confidential Information are bound by agreement to maintain such information in confidence and to use such information only as expressly permitted in this Agreement.

4.2 **Publication**. Notwithstanding any matter set forth in this Agreement to the contrary, results obtained in the course of the Research Program may be submitted for publication following scientific review by the Research Committee and subsequent written approval by both parties.

4.3 **Publicity**. The press release announcing the signing of the transaction contemplated by this Agreement is attached as Exhibit J hereto and shall be promptly disseminated by Isis following signing by both parties. Except as required by law or permitted in this Agreement, neither party may disclose the terms of this Agreement nor the research described in it without the prior written consent of the other party.

4.4 **Disclosure of Inventions**. Each party shall promptly inform the other in writing about all inventions that are conceived, made or developed in the course of carrying out the Research Program by employees of, or consultants to, either of them solely, or jointly with employees of, or consultants to, the other.

4.5 **Permitted Disclosure.** If either party is requested to disclose the other's Confidential Information in connection with a legal or administrative proceeding or is otherwise required by law to disclose the other's Confidential Information, such party will give the other party prompt written notice of such request. The party whose Confidential Information is to be disclosed may seek and pay for an appropriate protective order or other remedy or waive compliance with the provisions of this Agreement. If such party seeks a protective order or other remedy, the other party will cooperate. If such party fails to obtain a protective order or waive compliance with the relevant provisions of this Agreement, the other party will disclose only that portion of such party's Confidential Information which its legal counsel determines it is required to disclose. The parties agree that Isis will have the right to disclose the information required **[***]**.

5. Intellectual Property Rights. The following provisions relate to rights in the intellectual property developed by Isis, Pfizer, or both in performance of the Research Program.

5.1 **Ownership**. All Isis Confidential Information, Isis Technology, Isis Know-how, Isis Manufacturing Technology, Isis Manufacturing Know-how, **[***]**, Isis Technology Patent

Rights, Isis Manufacturing Patent Rights, and **[***]** shall be owned by Isis. All Pfizer Confidential Information and **[***]** shall be owned by Pfizer. Subject to Section 11, all Program Technology, Program Know-how, and Program Technology Patent Rights shall be owned by Pfizer.

5.2 **Grants of Research Licenses**.

(a) **Isis Research License**. Isis grants to Pfizer and its agents a non-exclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual license, to make and use **[***]**for all research purposes. Isis grants to Pfizer and its agents a non-exclusive, non-transferable, worldwide, royalty free license to make and use **[***]** under Isis' interests in **[***]**, to perform Pfizer's obligations under this Agreement.

(b) **Pfizer Research License**. Pfizer grants to Isis and its agents a nonexclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual license, to make and use **[***]**for all research purposes under Pfizer's interest in **[***]**.

(c) For clarity, this Section 5.2 does not grant either party or its agents any right to make and use the other's Confidential Information, **[***]** in the sale or manufacture for sale of products or processes. No additional rights are granted to agents of either party, except as expressly provided for herein.

5.3 **Assignment of [***]**. So long as **[***]**, upon Pfizer's written request but subject to Section 11, Isis will assign **[***]** to Pfizer. Upon assignment, **[***]** shall be deemed Program Technology, and **[***]** shall be deemed Program Technology Patent Rights.

6. Provisions Concerning the Filing, Prosecution and Maintenance of Patent Rights. Subject to Section 11 of this Agreement, the following provisions relate to the filing, prosecution and maintenance (and the cost thereof) of Program Technology Patent Rights and **[***]** during the term of this Agreement:

6.1 **Filing, Prosecution and Maintenance by Isis**. With respect to **[***]**, until the assignment described in Section 5.3, Isis shall have the exclusive right and (so long as **[***]**) obligation:

(a) to file applications for letters patent on any invention deemed patentable included in such Patent Rights; provided, however, that Isis shall consult with Pfizer regarding countries in which such patent applications should be filed and shall file patent applications in

those countries where Pfizer requests that Isis file such applications; and, further provided, that Isis, at its option and exercise, may file in countries where Pfizer does not request that Isis file such applications;

(b) to take all reasonable steps to prosecute all pending and new patent applications included within such Patent Rights;

(c) to respond to oppositions, nullity actions, re-examinations, revocation actions and similar proceedings filed by third parties against the grant of letters patent for such applications; and

(d) to maintain in force any letters patent included in such Patent Rights by duly filing all necessary papers and paying any fees required by the patent laws of the particular country in which such letters patent were granted.

6.2 **Filing, Prosecution and Maintenance by Pfizer**. With respect to Program Technology, Pfizer (using in-house or outside counsel, at its discretion) shall have the exclusive right and obligation:

(a) to file applications for letters patent on any invention deemed patentable included in the Program Technology; provided, however, that Pfizer shall consult with Isis as to the countries in which such patent applications should be filed;

(b) to take all reasonable steps to prosecute all pending and new patent applications included within Program Technology Patent Rights;

(c) to respond to oppositions, nullity actions, re-examinations, revocation actions and similar proceedings filed by third parties against the grant of letters patent for such applications;

(d) to maintain in force any letters patent included in Program Technology Patent Rights by duly filing all necessary papers and paying any fees required by the patent laws of the particular country in which such letters patent were granted; and Isis shall cooperate fully with, and take all necessary actions requested by, Pfizer in connection with the preparation, prosecution and maintenance of any letters patent included in Program Technology Patent Rights. Pfizer will reimburse Isis for reasonable expenses incurred for personnel travel and time spent out of office in connection with the foregoing.

(e) If Pfizer does not wish to exercise its right to file any application for letters patent on patentable inventions relating to the Program Technology, then Pfizer shall

provide Isis adequate written notice prior to any deadline with the U.S. Patent and Trademark Office or patent office of the **[***]** or **[***]**, and Isis will have the right to prepare and file such application(s) at its sole expense. Isis will solely own all related patent applications and letters patent issuing therefrom and grant Pfizer a nonexclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual research license under its rights to such patent applications and letters patent.

(f) Pfizer shall notify Isis in a timely manner of any decision to abandon a pending application or an issued patent included in Program Technology Patent Rights. Thereafter, Isis shall have the option, at its expense, of continuing to prosecute any such pending patent application or of keeping the issued patent in force. Isis will own all related patent applications and letters patent issuing therefrom and grant Pfizer a nonexclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual research license under its rights to such patent applications and letters patent.

6.3 **Copies of Documents**. Prior to filing, Isis shall provide to Pfizer copies of all patent applications that pursuant to Section 6.1 of this Agreement, Isis is obligated to file, prosecute and maintain, for the purpose of obtaining substantive comment of Pfizer's patent counsel. Each party (the "Prosecuting Party") shall provide to the other party every twelve (12) months a report detailing the status of all patent applications for which the Prosecuting Party is, under Section 6.1 or Section 6.2 of this Agreement, obligated to file, prosecute and maintain. Pfizer will have final authority on matters relating to patent applications and patents for which Pfizer will assume filing, prosecution and maintenance costs.

6.4 **Reimbursement of Costs for Filing, Prosecuting and Maintaining Patent Rights**. At least ninety (90) days prior to a patent filing deadline, Pfizer will notify Isis in writing of those countries in which Pfizer requests the **[***]**be filed, prosecuted and maintained. Within **[***]** (**[***]**) days of receipt of invoices from Isis, Pfizer shall reimburse Isis for all the costs of filing, prosecuting, responding to opposition and maintaining the **[***]**in countries where Pfizer requests that the **[***]** be filed, prosecuted and/or maintained, including costs incurred prior to the Effective Date. Such reimbursement shall be in addition to payments under Section 3. However, Pfizer may, upon **[***]** (**[***]**) days notice, request that Isis discontinue the filing, prosecution or maintenance of the Isis **[***]** in any country and discontinue reimbursing Isis for the costs of filing, prosecuting, responding to opposition or maintaining the **[***]** in such

country. Isis shall pay all costs in those countries in which Pfizer does not request that Isis file, prosecute or maintain the **[***]**, but in which Isis, at its option, elects to do so.

6.5 After the assignment described in Section 5.3, Pfizer shall have the right to file on behalf of and as an agent for Isis all applications and take all actions necessary to obtain patent extensions pursuant to 35 U.S.C. Section 156 and foreign counterparts for Patent Rights assigned under Section 5.3. Isis agrees to sign, at Pfizer's expense, such further documents and take such further actions as may be requested by Pfizer in this regard.

6.6 Neither party may disclaim a Valid Claim within Program Technology Patent Rights without the consent of the other.

6.7 **Bankruptcy.** All rights and licenses granted under or pursuant to any section of this Agreement are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101(35A) of the U.S. Bankruptcy Code. The parties shall retain and may fully exercise all of their respective rights and elections under the U.S. Bankruptcy Code. The parties agree that a party that is a licensee of such rights under this Agreement shall retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code, and that upon commencement of a bankruptcy proceeding by or against the licensing party (such party, the "Involved Party") under the U.S. Bankruptcy Code, the other party (such party, the "Noninvolved Party") shall be entitled to a complete duplicate of or complete access to (as such Noninvolved Party deems appropriate), any such intellectual property and all embodiments of such intellectual property, provided the Noninvolved Party continues to fulfill its payment or royalty obligations as specified herein in full. Such intellectual property and all embodiments thereof shall be promptly delivered to the Noninvolved Party (a) upon any such commencement of a bankruptcy proceeding upon written request therefore by the Noninvolved Party, unless the Involved Party elects to continue to perform all of its obligations under this Agreement or (b) if not delivered under (a) above, upon the rejection of this Agreement by or on behalf of the Involved Party upon written request therefor by the Noninvolved Party. The foregoing is without prejudice to any rights the Noninvolved Party may have arising under the U.S. Bankruptcy Code or other applicable law.

7. Acquisition of Rights from Third Parties. During the Contract Period, Isis and Pfizer will each promptly notify each other of any and all opportunities to acquire in any manner from

third parties, technology or patents or information which may be useful in or may relate to the Research Program. In the event Pfizer elects to license any such technology, patents or information (which election shall be in Pfizer's sole and absolute discretion), Pfizer will be responsible for such licenses (and payments thereunder). Isis is responsible for payments (if any) to maintain Isis' license to Isis Licensed Technology, until the respective expiration of the **[***]**. In the event Isis has acquired rights from a third party to any technology that Pfizer deems necessary or useful to the Research Program, Isis and Pfizer shall negotiate in good faith regarding a license to such technology on commercially reasonable terms, provided that Isis has the ability to grant such a license without violating the terms of any agreement or arrangement with such third party.

8. Other Agreements. Concurrently with the execution of this Agreement, Isis and Pfizer shall enter into the License Agreement appended to this Agreement as Exhibit H. This Agreement and the License Agreement are the sole agreements with respect to the subject matter and supersede all other agreements and understandings between the parties with respect to same.

9. Term, Termination and Disengagement.

9.1 **Term**. Unless sooner terminated or extended, this Agreement shall expire **[***]** from the Effective Date.

9.2 **Events of Termination**. The following events shall constitute events of termination ("Events of Termination"):

(a) Any material written representation or warranty by Isis or Pfizer made under or in connection with this Agreement shall prove to have been incorrect in any material respect when made.

(b) Isis or Pfizer shall fail in any material respect to perform or observe any material term, covenant or understanding contained in this Agreement or the License Agreement, and any such failure shall remain un-remedied for thirty (30) days after written notice to the failing party.

(c) If upon completion of the activities detailed in **[***]**, Pfizer may terminate this Agreement at any time thereafter.

(d) At any time, Pfizer may terminate this Agreement without cause upon **[***]** written notice to Isis.

(e) In the event that **[***]**, Pfizer will have the right at any time thereafter to terminate this Agreement upon **[***]** written notice to Isis.

9.3 **Termination**.

(a) Upon the occurrence of any Event of Termination described in Section 9.2(a) or 9.2(b), the party not responsible may, by written notice to the other party, terminate this Agreement.

(b) If either party terminates this Agreement pursuant to Section 9.3(a) or upon expiration of this Agreement pursuant to Section 9.1, the License Agreement shall continue according to its terms.

9.4 Termination of this Agreement in accordance with Sections 9.2(c), 9.2(d), 9.2(e), or 9.3(a) will not terminate the license granted pursuant to the first sentence of Section 5.2(a) or the license granted pursuant to Section 5.2(b).

9.5 Termination of this Agreement for any reason shall be without prejudice to:

(a) the rights and obligations of the parties set forth in any sections which provide by their terms for performance by either party subsequent to termination;

(b) Isis' right to receive all payments accrued under Section 3 and Section 6.4; or

(c) any other remedies which either party may otherwise have.

9.6 In the event that Pfizer terminates this Agreement pursuant to Section 9.2(d), **[***]**.

9.7 In the event that Pfizer terminates this Agreement pursuant to Section 9.2(e), subject to the payment obligations set forth in Section 3.3 (which section, as well as Section 3.5, will survive such termination), Isis grants to Pfizer and its agents a non-exclusive, non-transferable, worldwide, royalty free license to make and use Isis Technology, Isis Licensed Technology, Isis Know-how, and **[***]**under Isis' interests in Isis Technology Patent Rights, **[***]**, and Isis Licensed Technology Patent Rights, to perform research on and development of the ASOs discovered or developed by Isis in the course of the Research Program prior to the termination of the Agreement.

10. Loss of Target Exclusivity.

10.1 Section 2.3 will terminate and be of no further force or effect upon the occurrence of the earliest of any the following events:

(a) Upon termination of this Agreement by Pfizer pursuant to Section 9.2(c) or 9.2(d),

(b) Upon termination of this Agreement by Isis pursuant to Section 9.3(a) or Section 10.3 of the License Agreement,

(c) Upon expiration of the License Agreement,

(d) Upon termination of the License Agreement by Pfizer pursuant to Section 10.2(c) of the License Agreement.

10.2 Upon termination of Section 2.3 or substitution of **[***]**, Isis has the right to conduct research itself or sponsor any other research on the Exclusive Collaboration Gene Targets or removed **[***]**, as applicable, or engage in any research sponsored by any third party on the **[***]**, as applicable, without Pfizer's consent.

10.3 Pfizer may elect to designate any Exclusive Collaboration Gene Target as no longer subject to Section 2.3 by written notice to Isis. Such Exclusive Collaboration Gene Targets will no longer be subject to Section 2.3 upon the date of written notice by Pfizer.

11. Right of Reversion.

11.1 All Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products may transfer and revert to Isis and upon the assignment described in Section 11.3, all Program Technology and Program Know-how comprised of such pharmaceutical composition and/or use of ASOs and/or Products shall be deemed Isis Confidential Information, upon the earliest occurrence of any of the following events ("Reversion Trigger Events"):

(a) Upon termination of this Agreement by Pfizer pursuant to Section 9.2(c) or 9.2(d),

(b) Upon termination of this Agreement by Isis pursuant to Section 9.3(a),

(c) Upon termination of the License Agreement by Pfizer pursuant to Section 10.2(c) of the License Agreement.

(d) In addition, upon the substitution of **[***]**pursuant to Section 2.4, all Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products **[***]** may transfer and revert to Isis, and upon the assignment described in Section 11.3, all Program Technology and Program Know-how comprised of such pharmaceutical composition and/or use of ASOs and/or Products **[***]**shall be deemed Isis Confidential Information.

(e) At any time after the **[***]**, upon Isis' election by written notice to Pfizer, Pfizer shall promptly assign all Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products **[***]**to Isis, and upon the assignment described in Section 11.3, all Program Technology and Program Know-how comprised of such pharmaceutical composition and/or use of ASOs and/or Products **[***]** shall be deemed Isis Confidential Information.

11.2 Isis must provide written notice to Pfizer within **[***]** (**[***]**) days of any Reversion Trigger Event to inform Pfizer of its election to exercise the right of reversion.

11.3 Upon receipt of written notice by Isis to exercise its right of reversion, Pfizer shall promptly assign all Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products to Isis and thereafter Isis will have the exclusive right, but not the obligation, to prepare, file, prosecute, maintain and/or defend such Patent Rights.

11.4 Upon Pfizer's assignment of any Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products to Isis and any transfer or reversion of Program Know-how to Isis, Isis will grant Pfizer and its agents a non-exclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual license, to make and use such Patent Rights and Program Know-how for all research purposes.

11.5 Upon receipt of Isis' election to exercise its right of reversion, Pfizer shall promptly make available to and transfer one copy or assign to Isis the following: **[***]**. Both parties shall have the right to use such information as they see fit in the research, development and commercialization of products. **[***]**. Pfizer will also participate in a technical transfer meeting of no more than two days duration between the appropriate technical teams at Isis and Pfizer. Isis shall indemnify and hold Pfizer (and all officers, directors, employees, and agents of Pfizer) harmless for any and all damages, settlements, costs, legal fees and other expenses incurred in connection with a claim by a third party based on any action or omission of Isis, its agents, employees, or officers, related to or with regard to any use of such information or Isis'

development and commercialization of Products. Pfizer shall have no liability whatsoever for any inaccuracy or incompleteness in such information.

11.6 **[***]**.

12. Representations and Warranties. Isis and Pfizer each represents and warrants as follows:

12.1 It is a corporation duly organized, validly existing and is in good standing under the laws of the State of Delaware, is qualified to do business and is in good standing as a foreign corporation in each jurisdiction in which the conduct of its business or the ownership of its properties requires such qualification and has all requisite power and authority, corporate or otherwise, to conduct its business as now being conducted, to own, lease and operate its properties and to execute, deliver and perform this Agreement.

12.2 The execution, delivery and performance by it of this Agreement has been duly authorized by all necessary corporate action and do not and will not (a) require any consent or approval of its stockholders, (b) violate any provision of any law, rule, regulations, order, writ, judgment, injunction, decree, determination award presently in effect having applicability to it or any provision of its certificate of incorporation or by-laws or (c) result in a breach of or constitute a default under any material agreement, mortgage, lease, license, permit or other instrument or obligation to which it is a party or by which it or its properties may be bound or affected.

12.3 This Agreement is a legal, valid and binding obligation of it enforceable against it in accordance with its terms and conditions, except as such enforceability may be limited by applicable bankruptcy, insolvency, moratorium, reorganization or similar laws, from time to time in effect, affecting creditor's rights generally.

12.4 It is not under any obligation to any person, or entity, contractual or otherwise, that is conflicting or inconsistent in any respect with the terms of this Agreement or that would impede the diligent and complete fulfillment of its obligations hereunder.

12.5 It has good and marketable title to or valid leases or licenses for, all of its properties, rights and assets necessary for the fulfillment of its responsibilities under the Research Program, subject to no claim of any third party other than the relevant lessors or licensors.

12.6 Isis represents and warrants to Pfizer that:

(a) to its knowledge, as of the Effective Date, the issued Isis Technology Patent Rights and Isis Manufacturing Technology Patent Rights are valid and enforceable patents;

(b) to its knowledge, as of the Effective Date, the Isis Technology Patent Rights and Isis Manufacturing Technology Patent Rights are not subject to any pending re-examination, opposition, interference or litigation proceedings;

(c) as of the Effective Date, it has license rights to the Isis Licensed Technology Patent Rights;

(d) to its knowledge, as of the Effective Date, no additional third-party licenses (other than the Isis Licensed Technology) are required to practice Isis Technology and Isis Manufacturing Technology to discover, develop, commercialize and manufacture Products, except licenses that may be required related directly to the Exclusive Collaboration Gene Target down-regulated by a Product; and

(e) it has the right to grant the licenses granted and to convey the benefits of the covenants pursuant to this Agreement. Isis represents and warrants that the licenses so granted do not conflict with or violate the terms of any agreement between Isis and any third party.

13. Covenants of Isis and Pfizer Other Than Reporting Requirements. Throughout the Contract Period, Isis and Pfizer each shall:

(a) maintain and preserve its corporate existence, rights, franchises and privileges in the jurisdiction of its incorporation, and qualify and remain qualified as a foreign corporation in good standing in each jurisdiction in which such qualification is from time to time necessary or desirable in view of their business and operations or the ownership of their properties.

(b) comply in all material respects with the requirements of all applicable laws, rules, regulations and orders of any government authority to the extent necessary to conduct the Research Program.

14. Indemnification. Pfizer and Isis will indemnify, defend and hold each other harmless for any and all damages, settlements, costs, legal fees and other expenses incurred in connection with a claim by a third party against either party based on any action or omission of the indemnifying party's agents, employees, or officers related to its obligations under this Agreement; provided, however, that the foregoing shall not apply (i) if the claim is found to be based upon the negligence, recklessness or willful misconduct of the party seeking indemnification; or (ii) if such party fails to give the other party prompt notice of any claim it receives and such failure materially prejudices the other party with respect to any claim or action to which its obligation pursuant to this Section 14 applies. Further, Pfizer will indemnify, defend and hold Isis (and all officers, employees, consultants, directors, agents and Affiliates of Isis) harmless for any and all damages, settlements, costs, legal fees and other expenses incurred in connection with a claim by a third party against Isis based on the use by Isis of the Exclusive Collaboration Gene Targets or the **[***]**in accordance with the Research Plan. The indemnifying party, in its sole discretion, shall choose legal counsel, shall control the defense of such claim or action and shall have the right to settle same on such terms and conditions it deems advisable; provided, however, that any settlement includes, as an unconditional term thereof, a full release of the indemnified party from all liability with respect to such claim. Pfizer and Isis at all times reserve the right to retain counsel of its own to defend their respective interests.

15. Notices. All notices shall be deemed given as of the date received. All notices shall be made in writing, and mailed via certified mail, return receipt requested, courier, or facsimile transmission addressed as follows, or to such other address as may be designated from time to time:

If to Pfizer:
Pfizer Global R&D Headquarters
50 Pequot Avenue
New London, CT 06320
Attn.: Executive Vice President, PGRD
with copy to: General Counsel, PGRD

Invoices should be sent to the following address:

[***]
[***]
[***]
[***]
[***]

If to Isis:
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attn: Executive Vice President
With copy to: Vice-President, Legal

16. Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York.

17. Miscellaneous.

17.1 **Binding Effect**. This Agreement shall be binding upon and inure to the benefit of the parties and their respective legal representatives, successors and permitted assigns.

17.2 **Headings**. Paragraph headings are inserted for convenience of reference only and do not form a part of this Agreement.

17.3 **Counterparts**. This Agreement may be executed simultaneously in two or more counterparts, each of which shall be deemed an original. Signatures may be transmitted via facsimile; thereby constituting the valid signature and delivery of this Agreement.

17.4 **Amendment; Waiver**. This Agreement may be amended, modified, superseded or canceled, and any of the terms may be waived, only by a written instrument executed by each party or, in the case of waiver, by the party or parties waiving compliance. The delay or failure of any party at any time or times to require performance of any provisions shall in no manner affect the rights at a later time to enforce the same. No waiver by any party of any condition or of the breach of any term contained in this Agreement, whether by conduct, or otherwise, in any

one or more instances, shall be deemed to be, or considered as, a further or continuing waiver of any such condition or of the breach of such term or any other term of this Agreement.

17.5 **No Third Party Beneficiaries**. No third party including any employee of any party to this Agreement, shall have or acquire any rights by reason of this Agreement. Nothing contained in this Agreement shall be deemed to constitute the parties as partners with each other or any third party.

17.6 **Assignment and Successors**. This Agreement may not be assigned by either party, except that each party may assign this Agreement and the rights and interests of such party, in whole or in part, to any of its Affiliates, any purchaser of all or substantially all of its assets or outstanding stock or to any successor company resulting from any merger or consolidation of such party with or into such corporation; provided, however, that no Pfizer Confidential Information may be disclosed to any Isis acquirer or successor company as a result of a merger or consolidation involving Isis without Pfizer's prior written consent. Isis may assign its right to payment hereunder.

17.7 **Force Majeure**. Neither Pfizer nor Isis shall be liable for failure of or delay in performing obligations set forth in this Agreement, and neither shall be deemed in breach of its obligations, if such failure or delay is due to natural disasters or any causes reasonably beyond the control of Pfizer or Isis.

17.8 **Severability**. If any provision of this Agreement is or becomes invalid or is ruled invalid by any court of competent jurisdiction or is deemed unenforceable, it is the intention of the parties that the remainder of the Agreement shall not be affected so long as the essential benefits of this Agreement remains enforceable and obtainable.

17.9 **Survival of Terms.** In the event this Agreement expires or is terminated, certain terms that by their nature are intended to survive the expiration or termination of this Agreement, including but not limited to Sections 2.3, 2.8.3, 3.6, 4, 5.2, 9.5, 9.6 (and, by reference, Sections 3.2.1 and 3.5), 9.7 (and, by reference, Sections 3.3 and 3.5), 10, 11, 14, 15, 16 and 17, shall survive and remain in full force until expiration or termination by their respective terms.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives.

Pfizer Inc	**Isis Pharmaceuticals, Inc.**
By: /s/ John L. LaMattina	By: /s/ B. Lynne Parshall
Title: President, PGRD	Title: Executive Vice President & CFO
Date: 05/23/05	Date: 05/23/05

Exhibit List

Exhibit A

DEFINITIONS

1.1 **"Affiliate"** means any corporation or other legal entity owning, directly or indirectly, fifty percent (50%) or more of the voting capital shares or similar voting securities of Pfizer or Isis; any corporation or other legal entity fifty percent (50%) or more of the voting capital shares or similar voting rights of which is owned, directly or indirectly, by Pfizer or Isis; or any corporation or other legal entity fifty percent (50%) or more of the voting capital shares or similar voting rights of which is owned, directly or indirectly, by a corporation or other legal entity which owns, directly or indirectly, fifty percent (50%) or more of the voting capital shares or similar voting securities of Pfizer or Isis.

1.2 **"Area"** means research or development with respect to Products to inhibit expression of Exclusive Collaboration Gene Targets.

1.3 **"ASO"** means a non-self-complementary single-stranded oligonucleotide or analog thereof having a specific sequence that inhibits protein synthesis at the nucleic acid level by specifically binding to the sequence of a messenger or viral ribonucleic acid (RNA) by base-pairing, thus causing selective inhibition of gene expression, that (i) hybridizes to an Exclusive Collaboration Gene Target mRNA using **[***]** and (ii) down regulates an Exclusive Collaboration Gene Target utilizing **[***]** mechanism.

1.4 **"Commercially Reasonable Efforts"** means those efforts and resources that Pfizer would use were it developing or commercializing its own pharmaceutical products that are of similar market potential as the Licensed Products, taking into account product labeling, present and future market potential, past performance, financial return, present and future regulatory environment and competitive market conditions, all as measured by the facts and circumstances at the time such efforts are due.

1.5 **"Commitment Year"** means a twelve-month period commencing on the Effective Date and each anniversary of the Effective Date during the Contract Period.

1.6 **"Confidential Information"** means Isis Confidential Information and/or Pfizer Confidential Information, as the case may be.

1.7 **"Contract Period"** means the period beginning on the Effective Date and ending on the date on which the Research Agreement terminates or expires.

1.8 **"[***]"** means **[***]**.

1.9 **"Effective Date"** means May 24, 2005.

1.10 **"[***]"** means **[***]**,**[***]** corporation.

1.11 **"Exclusive Collaboration Gene Target"** means a target accepted by both parties to be introduced into the Research Plan. The Exclusive Collaboration Gene Targets accepted by both parties upon initiation of the Research Program are listed in Exhibit B to the Research Agreement.

1.12 **"[***]"** means **[***]**.

1.13 **"Isis Confidential Information"** means all information which is disclosed by Isis to Pfizer and designated "Confidential" in writing by Isis at the time of disclosure to Pfizer to the extent that such information is not (i) as of the date of disclosure to Pfizer, known to Pfizer other than by virtue of a prior confidential disclosure to Pfizer by Isis; or (ii) disclosed in published literature, or otherwise generally known to the public through no fault or omission of Pfizer; or (iii) obtained by Pfizer from a third party free from any obligation of confidentiality to Isis.

1.14 **"[***]"** means **[***]**.

1.15 **"[***]"** means all Patent Rights that claim **[***]** listed in Exhibit D to the Research Agreement.

1.16 **"Isis Know-how"** means Know-how introduced into the Research Program by Isis.

1.17 **"Isis Licensed Technology"** means the Technology acquired by Isis **[***]**.

1.18 **"Isis Licensed Technology Patent Rights"** means all Patent Rights that claim Isis Licensed Technology listed in Exhibit E to the Research Agreement.

1.19 **"Isis Manufacturing Know-how"** means **[***]**.

1.20 **"Isis Manufacturing Technology"** means **[***]**.

1.21 **"Isis Manufacturing Technology Patent Rights**" means Patent Rights controlled by Isis listed in Exhibit F to the Research Agreement that claim Isis Manufacturing Technology.

1.22 **"Isis Technology"** means Technology **[***]**.

1.23 **"Isis Technology Patent Rights"** means all Patent Rights that claim **[***]** listed in Exhibit G to the Research Agreement.

1.24 **"Know-how"** means know-how, expertise, and trade secrets that are held in confidence by either party.

1.25 **"License Agreement"** means the License and Royalty Agreement entered into by Pfizer and Isis and attached to the Research Agreement as Exhibit H.

1.26 **"Licensed Product"** means any Product the manufacture, use, sale, offer for sale or import of which, but for the grant of licenses in the Research Agreement or License Agreement and without regard to inventorship, would infringe any Valid Claim within Program Technology Patent Rights, Isis Technology Patent Rights, Isis Licensed Technology Patent Rights or **[***]**.

1.27 **"Net Sales"** means with respect to a Licensed Product, gross sales of Pfizer (including its Affiliates) and its licensees of such Licensed Product to parties that are not Affiliates (unless such Affiliate is the ultimate end-user of such Licensed Product), less (i) bad debts related to such Licensed Product and (ii) sales returns and allowances, including, without limitation, trade, quantity and cash discounts and any other reductions, including, but not

limited to, granted on account of price reductions, billing errors, rejected goods, damaged or defective goods, recalls, returns, rebates, chargeback rebates, reimbursements or similar payments granted or given to wholesalers or other distributors, buying groups, health care insurance carriers or other institutions, reductions arising from consumer discount programs, including without limitation the Pfizer ShareCard, customs or excise duties, sales tax, consumption tax, valued added tax, and other taxes (except income taxes) or duties relating to sales, any payment in respect of sales to any Governmental Authority in respect of any government-subsidized program, [and freight and insurance (to the extent that Pfizer bears the cost of freight and insurance for a Licensed Product)]. For clarity, such sales shall not include units distributed for free (a) as samples, (b) for use in clinical trials or (c) for humanitarian or compassionate use.

1.28 **"Patent Rights"** means all patent rights in and to inventions including all the claims of patent applications and/or patents, whether domestic or foreign, claiming such inventions, including all continuations, continuations-in-part, divisions, and renewals, and letters of patent granted thereon, and all reissues, re-examination and extensions thereof.

1.29 **"Pfizer Confidential Information"** means all information which is disclosed by Pfizer to Isis and designated "Confidential" in writing by Pfizer at the time of disclosure to Isis to the extent that such information is not (i) known, as of the date of disclosure to Isis, other than by virtue of a prior confidential disclosure to Isis by Pfizer; or (ii) disclosed in published

literature, or otherwise generally known to the public through no fault or omission of Isis; or (iii) obtained by Isis from a third party free from any obligation of confidentiality to Pfizer.

1.30 **"[***]"** means **[***]**.

1.31 **"Product"** means any product for the treatment or prevention of human health disease, comprising any single ASO, or combination of non-complementary ASOs thereof, generated under the Research Plan.

1.32 **"Program Know-how"** means Know-how that is or was developed by employees of or consultants to Pfizer or Isis solely or jointly with each other in performance of the Research Program.

1.33 **"Program Technology"** means (a) Technology that is or was developed by employees or agents of or consultants to Pfizer or Isis solely or jointly with each other in performance of the Research Program and, (b) upon the assignment described in Section 5.3 of the Research Agreement, **[***]**.

1.34 **"Program Technology Patent Rights"** means all Patent Rights that claim Program Technology.

1.35 **"Research Agreement"** means the Collaborative Research Agreement between Pfizer and Isis effective May 24, 2005.

1.36 **"Research Plan"** means the written plan describing the research in the Area to be carried out during each Commitment Year by Pfizer and Isis pursuant to the Research Agreement. Each revision to the Research Plan will be attached to and made a part of the Research Agreement as an amendment to Exhibit I to the Research Agreement.

1.37 **"Research Program"** is the collaborative research program in the Area conducted by Pfizer and Isis during the Contract Period pursuant to the Research Plan.

1.38 **"Technology"** means and includes all materials, technology, and technical information covered by Patent Rights.

1.39 **"Valid Claim"** means an unexpired issued claim (including any extension pursuant to, inter alia, 35 U.S.C. 154(b) and 156 (the Patent Term Restoration Act)) within Patent Rights which has not been held invalid or unenforceable by a final decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable by the owner through reissue or disclaimer. If there should be two or more such decisions conflicting

with respect to the validity of the same claim the decision of the higher or highest tribunal shall thereafter control; however, should the tribunals be of equal dignity the decision or decisions holding the claim invalid should prevail.

Exhibit B

Exclusive Collaboration Gene Targets

[***]

Exhibit C

[***]

[***]

Exhibit D

[***]

[***]

Exhibit E

Isis Licensed Technology Patent Rights

[***]

Exhibit F

Isis Manufacturing Technology Patent Rights

[***]

Exhibit G

Isis Technology Patent Rights

[***]

Exhibit H

LICENSE AND ROYALTY AGREEMENT

This **LICENSE AND ROYALTY AGREEMENT ("Agreement")** is entered into as of May 24, 2005 (the "Effective Date") by and between **PFIZER INC** and its Affiliates ("Pfizer"), a Delaware corporation, having an office at 235 East 42nd Street, New York, New York 10017 and **ISIS PHARMACEUTICALS, INC.** ("Isis"), a Delaware corporation, having an office at 1896 Rutherford Road, Carlsbad, CA 92008;

WHEREAS, Pfizer desires to obtain an exclusive license under Isis' right, title and interest in the Isis Technology, Isis Technology Patent Rights, Isis Licensed Technology, Isis Licensed Technology Patent Rights, **[***]**, and **[***]**, so that Pfizer can manufacture, use, sell, offer for sale and import the Licensed Products; and

WHEREAS, Isis is willing to grant such license;

Therefore, in consideration of the mutual covenants and promises set forth in this Agreement, the parties agree as follows:

1. Definitions. The capitalized terms used in this Agreement, and not defined elsewhere in it, shall have the meanings specified for such terms in Exhibit A of the Research Agreement.

2. Grant of Licenses, Term, Rights and Obligations.

2.1 **Licenses Granted to Pfizer.** Isis hereby grants to Pfizer an exclusive, worldwide license, including the right to grant sublicenses, to manufacture, use, sell, offer for sale and import Licensed Products under all Isis' right, title and interest in the Isis Technology Patent Rights, **[***]**, and Isis Licensed Technology Patent Rights. In addition, Isis grants to Pfizer an exclusive, worldwide license, excluding the right to grant sublicenses, to manufacture Licensed

Products under all Isis' right, title and interest in the Isis Manufacturing Technology, Isis Manufacturing Know-how, and Isis Manufacturing Technology Patent Rights. The licenses granted are contingent upon Pfizer fulfilling its payment obligations to Isis under Section 3.3 of the Research Agreement and Section 3 of this Agreement and do not become effective until, with respect to each Licensed Product, Pfizer has made the payment set forth in Section 3.3(d) of the Research Agreement.

2.2 **Assignment of [***]**. So long as **[***]**, upon Pfizer's written request but subject to Section 12, Isis will assign **[***]** to Pfizer. Upon assignment, **[***]** shall be considered Program Technology, and **[***]** shall be considered a part of Program Technology Patent Rights.

2.3 **Term of Licenses**. The term of the licenses set forth in Section 2.1 shall commence on the Effective Date. The licenses granted in Section 2.1 to Pfizer under all Isis' right, title and interest in Isis Technology Patent Rights, **[***]**, and Isis Licensed Technology Patent Rights shall terminate, on a country-by-country basis, upon the date of expiration of each such Patent Right.

2.4 **Paid-Up License**. Upon the expiration of each of Isis Technology Patent Rights, **[***]**, and Isis Licensed Technology Patent Rights, Pfizer shall have a paid-up, royalty-free non-exclusive license to each such Patent Right. If Pfizer desires to offer for sale Licensed Products in countries in which the Royalty Payment Term set forth in Section 3.1.1 has expired and such Licensed Products are manufactured in a country in which they are not covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, using a manufacturing process covered by a Valid Claim in Isis Manufacturing Technology Patent Rights, Pfizer and Isis shall negotiate in good faith regarding a license to such rights on commercially reasonable terms. **[***]**.

2.5 **[***]**. **[***]**, Pfizer and Isis shall negotiate in good faith for a license to such technology on commercially reasonable terms; provided, however, that Isis has the ability to grant such license without violating the terms of any agreement or other arrangement with any third party at the time such license is granted.

2.6 **Pfizer Obligations.**

2.6.1 Pfizer shall attempt to develop and commercialize **[***]** using Commercially Reasonable Efforts. Pfizer will have sole authority and discretion to make all decisions relating to the development and commercialization (including termination) of Licensed

Products.

2.6.2 If Pfizer grants a sublicense pursuant to this Section 2, Pfizer shall guarantee that any sublicensee fulfills all of Pfizer's obligations under this Agreement; provided, however, that Pfizer shall not be relieved of its obligations pursuant to this Agreement.

2.7 **Technical Assistance.** Isis shall provide to Pfizer or any sublicensee of Pfizer, at Pfizer's request and expense, during normal business hours and upon reasonable advance notice and request, any technical assistance reasonably necessary to enable Pfizer or such sub-licensee to manufacture, use, sell, offer for sale or import each Licensed Product and to enjoy fully all the rights granted to Pfizer pursuant to this Agreement; provided however, that Isis is reasonably capable of providing that assistance and the terms upon which such assistance shall be provided are mutually agreeable to Isis and Pfizer.

2.8 **Research License**. Isis grants to Pfizer and its agents a non-exclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual license, to make and use Isis Know-how for all research purposes. Isis grants to Pfizer and its agents a non-exclusive, non-transferable, worldwide, royalty free license to make and use Isis Technology, Isis Know-how, Isis Licensed Technology, and **[***]** under Isis' interests in Isis Technology Patent Rights, Isis Know-how, **[***]**, and Isis Licensed Technology Patent Rights, to perform Pfizer's obligations under this Agreement.

3. Milestone Payments, Royalties, Accounting, Records.

3.1 **Royalty Payment Term.** Pfizer shall pay Isis a royalty based on the Net Sales of each Licensed Product.

3.1.1 In countries in which such Licensed Product is covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, a royalty shall be paid with respect to each such country from the date of first commercial sale (the date of the invoice of Pfizer or any sublicense of Pfizer with respect to such sale) of such Licensed Product in such country until the date on which such Licensed Product is no longer covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights in such country ("Royalty Payment Term").

3.1.2 If a Licensed Product is sold in countries in which such Licensed Product is not

covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, and such Licensed Product is manufactured in a country in which it is covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, Pfizer shall pay Isis a **[***]** royalty based on the Net Sales of such Licensed Product pursuant to Section 3.2.2.

3.2 **Royalty Rates.**

3.2.1 In all countries in which a Licensed Product is covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, the royalty paid by Pfizer to Isis shall be **[***]** percent (**[***]**%) of Net Sales for such Licensed Product in such country.

3.2.2 In countries in which a Licensed Product is not covered by a Valid Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights and such Licensed Product is manufactured in a country in which it is covered by a Valid

Claim in Program Technology Patent Rights, Isis Technology Patent Rights, **[***]** or Isis Licensed Technology Patent Rights, the royalty paid by Pfizer to Isis shall be **[***]** percent (**[***]**%) of Net Sales for such Licensed Product in such country.

3.3 **Sales Milestones.** Pfizer shall pay Isis the following sales milestones: (a) **[***]** dollars ($**[***]**) upon the achievement by a Licensed Product of cumulative Net Sales of **[***]** dollars ($**[***]**) for **[***]** and (b) **[***]** dollars ($**[***]**) upon the achievement by a Licensed Product of cumulative Net Sales of **[***]** dollars ($**[***]**) for **[***]**. Pfizer shall be obligated to pay these milestones **[***]**. Pfizer shall be obligated to pay these milestones with respect to **[***]**. **[***]**.

3.4 **Payment Dates.** Royalties shall be paid by Pfizer on Net Sales within **[***]** (**[***]**) days after the end of each calendar quarter in which such Net Sales are made. Such payments shall be accompanied by a statement showing the Net Sales of each Licensed Product by Pfizer or any sublicensee of Pfizer in each country, the applicable royalty rate for such Licensed Product in each country, and a calculation of the amount of royalty due, including any offsets and where each such Licensed Product was manufactured.

3.5 **Royalty and Sales Milestone Computation and Payment.** The Net Sales used for computing the royalties and sales milestones payable to Isis by Pfizer shall be computed and paid in US dollars by wire transfer in immediately available funds to a U.S. account designated

by Isis, or by other mutually acceptable means. For purposes of determining the amount of royalties due, the amount of Net Sales in any foreign currency shall be computed by converting such amount into U.S. dollars at the prevailing commercial rate of exchange for purchasing dollars with such foreign currency as published in the *Wall Street Journal* for the close of the last business day of the calendar quarter for which the relevant royalty payment is to be made by Pfizer. For purposes of determining whether a sales milestone (as set forth in Section 3.3) has been achieved, the amount of Net Sales in any foreign currency shall be computed by converting such amount into U.S. dollars at the prevailing commercial rate of exchange for purchasing dollars with such foreign currency as published in the *Wall Street Journal* for the close of the last business day of the calendar quarter for which such Net Sales are made.

3.6 **Records.** Pfizer shall keep for **[***]** (**[***]**) years from the date of each payment of royalties complete and accurate records of sales by Pfizer and its sublicensees of each Licensed Product, as well as any offsets, in sufficient detail to allow the accruing royalties to be determined accurately. Isis shall have the right for a period of **[***]** (**[***]**) years after receiving any report or statement with respect to royalties due and payable to appoint an independent certified public accountant reasonably acceptable to Pfizer to inspect the relevant records of Pfizer to verify such report or statement. Pfizer shall make its records available for inspection by such independent certified public accountant during regular business hours at such place or places where such records are customarily kept, upon reasonable notice from Isis, to verify the accuracy of the reports and payments. Such inspection right shall not be exercised more than once in any calendar year nor more than once with respect to sales in any given period. Isis agrees to hold in strict confidence all information concerning royalty payments and reports, and all information learned in the course of any audit or inspection, except to the extent necessary for Isis to reveal such information in order to enforce its rights under this Agreement or if disclosure is required by law. The failure of Isis to request verification of any report or statement during said **[***]**-year period shall be considered acceptance of the accuracy of such report, and Pfizer shall have no obligation to maintain records pertaining to such report or statement beyond said **[***]**-year period. The findings of each inspection, if any, shall be binding on both parties. The cost of such inspection will be borne by Isis, unless such inspection discloses an underpayment of more than **[***]** percent (**[***]**%) from the amount of Net Sales or royalties or other payments

due under this Agreement. In such case, (a) the cost of such inspection shall be borne by Pfizer and Pfizer will promptly remit the amount of such underpayment and (b) such inspection will not count as the exercise of an inspection right.

3.7 **Development Milestone Payments**. On **[***]** basis, Pfizer shall pay Isis, within **[***]** (**[***]**) days of the date of each event set forth below ("Event"), the payment listed opposite that Event with respect to Licensed Products which selectively inhibit a particular Exclusive Collaboration Gene Target. Payments shall be made in U.S. dollars by wire transfer in immediately available funds to a U.S. bank account designated by Isis, or other mutually acceptable means. Pfizer shall be obligated to pay such milestones **[***]**. **[***]**. All development milestone payments made by Pfizer for **[***]** with respect to a Licensed Product shall be **[***]**. All development milestone payments made by Pfizer for **[***]** with respect to a Licensed Product shall be **[***]**.

In the event that a Licensed Product is approved for multiple indications in the U.S., the parties agree that Pfizer will as appropriate use data from an external physician audit such as that conducted by Scott-Levin or IMS to measure the extent to which physicians recommend the use of the Licensed Product in conjunction with patient visits for specifically coded and identified medical conditions (ICD-9 codes). The appropriate ICD-9 code or codes for such data will be adopted by the parties within three (3) months, or as soon thereafter as Scott-Levin or IMS provides relevant coding information, of the first sale of a Licensed Product in the United States for the indications in question. **[***]**.

In the event that a Licensed Product is approved for multiple indications in countries outside the U.S., the parties will establish appropriate procedures for measuring sales of the Licensed Product for the indications in question within six (6) months of the first sale of the Licensed Product in such countries for the indications in question.

Event		Amount	
1.	**[***]**	**$**	[***]
2.	**[***]**	$	[***]
3.	**[***]**	**$**	[***]

4.	**[***]**	**$**	[***]
5.	**[***]**	**$**	[***]
6.	**[***]**	**$**	[***]
7.	**[***]**	**$**	[***]
8.	**[***]**	**$**	[***]

For the purposes of the foregoing, "IND" shall mean an Investigational New Drug Application filed with the U.S. FDA, or a similar filing made with a counterpart health regulatory authority in another country; "NDA/PLA" shall mean a New Drug Application, Product License Application, or other application for authority to market a Licensed Product filed with the U.S. FDA or a counterpart health regulatory agency in another country.

3.8 **Safety Database**. Isis maintains a database that includes information regarding the tolerability of its compounds, individually and as a class, including information discovered during clinical development (the "Isis Database"). Pfizer will consider entering into an agreement with Isis under which Pfizer will (a) cooperate in connection with populating the Isis Database, (b) provide Isis with copies of toxicology, pharmacokinetic and serious adverse event reports related to ASOs and (c) in connection with any reported serious adverse event, provide mutually agreed to patient data regarding such event. Pfizer is not under any obligation to enter into such an agreement.

4. Third Party Manufacture of Licensed Product. In the event Pfizer decides to seek a third party to manufacture clinical or commercial supplies of the Licensed Product, Isis shall have the right to bid on any such contract.

5. Legal Action.

5.1 **Actual or Threatened Disclosure or Infringement.** Isis will cooperate with Pfizer, at Pfizer's expense, in any action taken by Pfizer to prevent unlawful infringement of Program Technology Patent Rights.

5.2 **Defense of Infringement Claims.** Isis will cooperate with Pfizer at Pfizer's expense in the defense of any suit, action or proceeding against Pfizer or any sublicensee of Pfizer alleging the infringement of the intellectual property rights of a third party by reason of the use of Program Technology Patent Rights, Program Know-how, **[***]**, Isis Licensed Technology Patent Rights, Isis Manufacturing Technology Patent Rights, Isis Manufacturing Know-how, or Isis Technology Patent Rights in the manufacture, use or sale of a Licensed Product. Pfizer shall give Isis prompt written notice of the commencement of any such suit, action or proceeding or claim of infringement and will furnish Isis a copy of each communication relating to the alleged infringement. With respect to a suit, action or proceeding against Pfizer or any sublicensee related solely to the use of Program Technology or Program Know-how, and subject to Section 12, Isis shall give to Pfizer all authority (including the right to exclusive control of the defense of any such suit, action or proceeding) and the exclusive right after consultation with Isis, to compromise, litigate, settle or otherwise dispose of any such suit, action or proceeding, at Pfizer's expense, including by providing information and assistance necessary to defend or settle any such suit, action or proceeding; provided, however, Pfizer shall obtain Isis' prior written consent to such part of any settlement which contemplates payment or other action by Isis or has a material adverse effect on Isis' business. With respect to any suit, action or proceeding against Pfizer or any sublicensee related solely or partially to the use of Isis Technology Patent Rights, Isis Manufacturing Technology Patent Rights, Isis Licensed Technology Patent Rights, **[***]** prior to assignment to Pfizer, Isis Know-how, Isis Manufacturing Know-how or Isis Manufacturing Technology, Isis will actively participate in the planning and conduct of such suit, action or proceeding, and Pfizer will not, without the express prior written consent of Isis, (a) make any substantive decision regarding strategy related to such suit, action or proceeding or (b) settle such suit, action or proceeding. If the parties agree that Isis should institute or join any suit, action or proceeding pursuant to this Section, Pfizer may, at Pfizer's expense, join Isis as a defendant if necessary or desirable, and Isis shall execute all

documents and take all other actions, including giving testimony, which may reasonably be required in connection with the prosecution of such suit, action or proceeding.

5.3 **Hold Harmless.** Isis agrees to defend, indemnify and hold harmless Pfizer and any sublicensee of Pfizer, from and against any loss or expense arising from any claim of a third party that Isis did not have the right to grant Pfizer the licenses set forth in Section 2.1 of this Agreement and such third party's rights are being infringed upon by reason of Pfizer or any sublicensee of Pfizer exercising their rights granted to Pfizer by Isis pursuant to this Agreement.

5.4 **Third Party Licenses.** Isis is responsible for payments to maintain Isis' licenses to Isis Licensed Technology, until the respective expiration of the **[***]**. Subject to Section 6.5(d), **[***]** Licensed Products.

6. Representation and Warranty. Isis and Pfizer each represents and warrants as follows:

6.1 It is a corporation duly organized, validly existing and is in good standing under the laws of the State of Delaware, is qualified to do business and is in good standing as a foreign corporation in each jurisdiction in which the conduct of its business or the ownership of its properties requires such qualification and has all requisite power and authority, corporate or otherwise, to conduct its business as now being conducted, to own, lease and operate its properties and to execute, deliver and perform this Agreement.

6.2 The execution, delivery and performance by it of this Agreement has been duly authorized by all necessary corporate action and do not and will not (a) require any consent or approval of its stockholders, (b) violate any provision of any law, rule, regulations, order, writ, judgment, injunction, decree, determination award presently in effect having applicability to it or any provision of its certificate of incorporation or by-laws or (c) result in a breach of or constitute a default under any material agreement, mortgage, lease, license, permit or other instrument or obligation to which it is a party or by which it or its properties may be bound or affected.

6.3 This Agreement is a legal, valid and binding obligation of it enforceable against it in accordance with its terms and conditions, except as such enforceability may be limited by applicable bankruptcy, insolvency, moratorium, reorganization or similar laws, from time to time in effect, affecting creditor's rights generally.

6.4 It is not under any obligation to any person, or entity, contractual or otherwise, that is conflicting or inconsistent in any respect with the terms of this Agreement or that would impede the diligent and complete fulfilment of its obligations hereunder.

6.5 Isis represents and warrants to Pfizer that:

(a) to its knowledge, as of the Effective Date, the issued Isis Technology Patent Rights and Isis Manufacturing Technology Patent Rights are valid and enforceable patents;

(b) to its knowledge, as of the Effective Date, the Isis Technology Patent Rights and Isis Manufacturing Technology Patent Rights are not subject to any pending re-examination, opposition, interference or litigation proceedings;

(c) as of the Effective Date, it has license rights to the Isis Licensed Technology Patent Rights;

(d) to its knowledge, as of the Effective Date, no additional third-party licenses (other than the Isis Licensed Technology) are required to practice Isis Technology and Isis Manufacturing Technology to discover, develop, commercialize and manufacture Products, except licenses that may be required related directly to the Exclusive Collaboration Gene Target down-regulated by a Product; and

(e) it has the right to grant the licenses granted and to convey the benefits of the covenants pursuant to this Agreement. Isis represents and warrants that the licenses so granted do not conflict with or violate the terms of any agreement between Isis and any third party.

7. Treatment of Confidential Information.

7.1 **Confidentiality**.

(a) Subject to permitted disclosure under Sections 7.1(c) and 7.1(e), Pfizer and Isis each agree that during the term of this Agreement and for **[***]** thereafter, it will keep confidential all Isis Confidential Information or Pfizer Confidential Information, as the case may be, that is disclosed to it, or to any of its Affiliates, pursuant to this Agreement. Subject to Section 12, Program Technology and Program Know-how shall be deemed Pfizer Confidential Information.

(b) Neither Pfizer nor Isis shall use the other's Confidential Information except as expressly permitted in this Agreement.

(c) Pfizer and Isis each agree that any disclosure of the other's Confidential Information to any of its officers, employees, agents or Affiliates shall be made only if and to the extent necessary to carry out its responsibilities under this Agreement and shall be limited to the maximum extent possible consistent with such responsibilities. Pfizer and Isis each agree not to disclose the other's Confidential Information to any individual, entity or party for whom disclosure is not expressly permitted under this Section, under any circumstance without written permission from the other party. Each party shall take such action to preserve the confidentiality of each other's Confidential Information as it would customarily take to preserve the confidentiality of its own Confidential Information. Each party, upon the other's request, will return all the Confidential Information disclosed to the other party pursuant to this Agreement, including all copies and extracts of documents, within sixty (60) days of the request upon the termination of this Agreement except for one (1) copy which may be kept for the purpose of complying with continuing obligations under this Agreement.

(d) Isis and Pfizer each represent that all of its employees, Affiliates, agents, and any consultants to such party, who shall have access to **[***]**, Isis Technology, Isis Know-how, Isis Manufacturing Technology, Isis Manufacturing Know-how, **[***]**, Isis Licensed Technology, Program Technology, Program Know-how, Pfizer Confidential Information or Isis Confidential Information are bound by agreement to maintain such information in confidence and to use such information only as expressly permitted in this Agreement.

(e) **Permitted Disclosure.** If either party is requested to disclose the other's Confidential Information in connection with a legal or administrative proceeding or is otherwise required by law to disclose the other's Confidential Information, such party will give the other party prompt written notice of such request. The party whose Confidential Information is to be disclosed may seek and pay for an appropriate protective order or other remedy or waive compliance with the provisions of this Agreement. If such party seeks a protective order or other remedy, the other party will cooperate. If such party fails to obtain a protective order or waive compliance with the relevant provisions of this Agreement, the other party will disclose only that portion of such party's Confidential Information which its legal counsel determines it is required

to disclose. The parties agree that Isis will have the right to disclose the information required **[***]**.

7.2 **Publicity**. Except as required by law or permitted in this Agreement, neither party may disclose the terms of this Agreement without the prior written consent of the other party. Pfizer agrees that Isis may use information made public by Pfizer on the development status of the Licensed Products in the product/partner pipeline on its website.

8. Provisions Concerning the Filing, Prosecution and Maintenance of Patent Rights. Subject to Section 12 of this Agreement, the following provisions relate to the filing, prosecution and maintenance (and the cost thereof) of Program Technology Patent Rights and **[***]** during the term of this Agreement:

8.1 **Filing, Prosecution and Maintenance by Isis**. With respect to **[***]**, until the assignment described in Section 2.2, , Isis shall have the exclusive right and (so long as **[***]**) obligation:

(a) to file applications for letters patent on any invention deemed patentable included in such Patent Rights; provided, however, that Isis shall consult with Pfizer regarding countries in which such patent applications should be filed and shall file patent applications in those countries where Pfizer requests that Isis file such applications; and, further provided, that Isis, at its option and exercise, may file in countries where Pfizer does not request that Isis file such applications;

(b) to take all reasonable steps to prosecute all pending and new patent applications included within such Patent Rights;

(c) to respond to oppositions, nullity actions, re-examinations, revocation actions and similar proceedings filed by third parties against the grant of letters patent for such applications; and

(d) to maintain in force any letters patent included in such Patent Rights by duly filing all necessary papers and paying any fees required by the patent laws of the particular country in which such letters patent were granted.

8.2 **Filing, Prosecution and Maintenance by Pfizer**. With respect to Program Technology, Pfizer (using in-house or outside counsel, at its discretion) shall have the exclusive right and obligation:

(a) to file applications for letters patent on any invention deemed patentable included in the Program Technology; provided, however, that Pfizer shall consult with Isis as to the countries in which such patent applications should be filed;

(b) to take all reasonable steps to prosecute all pending and new patent applications included within Program Technology Patent Rights;

(c) to respond to oppositions, nullity actions, re-examinations, revocation actions and similar proceedings filed by third parties against the grant of letters patent for such applications;

(d) to maintain in force any letters patent included in Program Technology Patent Rights by duly filing all necessary papers and paying any fees required by the patent laws of the particular country in which such letters patent were granted; and Isis shall cooperate fully with, and take all necessary actions requested by, Pfizer in connection with the preparation, prosecution and maintenance of any letters patent included in Program Technology Patent Rights. Pfizer will reimburse Isis for reasonable expenses incurred for personnel travel and time spent out of office in connection with the foregoing.

(e) If Pfizer does not wish to exercise its right to file any application for letters patent on patentable inventions relating to the Program Technology, then Pfizer shall provide Isis adequate written notice prior to any deadline with the U.S. Patent and Trademark Office or patent office of the **[***]** or **[***]**, and Isis will have the right to prepare and file such application(s) at its sole expense. Isis will solely own all related patent applications and letters patent issuing therefrom and grant Pfizer a nonexclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual research license under its rights to such patent applications and letters patent.

(f) Pfizer shall notify Isis in a timely manner of any decision to abandon a pending application or an issued patent included in Program Technology Patent Rights. Thereafter, Isis shall have the option, at its expense, of continuing to prosecute any such pending patent application or of keeping the issued patent in force. Isis will own all related patent applications and letters patent issuing therefrom and grant Pfizer a nonexclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual research license under its rights to such patent applications and letters patent.

8.3 **Copies of Documents**. Prior to filing, Isis shall provide to Pfizer copies of all patent applications that pursuant to Section 8.1 of this Agreement, Isis is obligated to file, prosecute and maintain, for the purpose of obtaining substantive comment of Pfizer's patent counsel. Each party (the "Prosecuting Party") shall provide to the other party every twelve (12) months a report detailing the status of all patent applications for which the Prosecuting Party is, under Section 8.1 or Section 8.2 of this Agreement, obligated to file, prosecute and maintain. Pfizer will have final authority on matters relating to patent applications and patents for which Pfizer will assume filing, prosecution and maintenance costs.

8.4 **Reimbursement of Costs for Filing, Prosecuting and Maintaining Patent Rights**. At least ninety (90) days prior to a patent filing deadline, Pfizer will notify Isis in writing of those countries in which Pfizer requests the **[***]** be filed, prosecuted and maintained. Within **[***]** (**[***]**) days of receipt of invoices from Isis, Pfizer shall reimburse Isis for all the costs of filing, prosecuting, responding to opposition and maintaining the **[***]** in countries where Pfizer requests that the **[***]** be filed, prosecuted and/or maintained, including costs incurred prior to the Effective Date. Such reimbursement shall be in addition to payments under Section 3. However, Pfizer may, upon **[***]** (**[***]**) days notice, request that Isis discontinue the filing, prosecution or maintenance of the **[***]** in any country and discontinue reimbursing Isis for the costs of filing, prosecuting, responding to opposition or maintaining the **[***]** in such country. Isis shall pay all costs in those countries in which Pfizer does not request that Isis file, prosecute or maintain the **[***]**, but in which Isis, at its option, elects to do so.

8.5 After the assignment described in Section 2.2, Pfizer shall have the right to file on behalf of and as an agent for Isis all applications and take all actions necessary to obtain patent extensions pursuant to 35 U.S.C. Section 156 and foreign counterparts for Patent Rights assigned under Section 2.2. Isis agrees to sign, at Pfizer's expense, such further documents and take such further actions as may be requested by Pfizer in this regard.

8.6 Neither party may disclaim a Valid Claim within Program Technology Patent Rights without the consent of the other.

8.7 **Bankruptcy.** All rights and licenses granted under or pursuant to any section of this Agreement are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101(35A) of the U.S. Bankruptcy Code. The parties shall retain and may fully exercise all of

their respective rights and elections under the U.S. Bankruptcy Code. The parties agree that a party that is a licensee of such rights under this Agreement shall retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code, and that upon commencement of a bankruptcy proceeding by or against the licensing party (such party, the "Involved Party") under the U.S. Bankruptcy Code, the other party (such party, the "Noninvolved Party") shall be entitled to a complete duplicate of or complete access to (as such Noninvolved Party deems appropriate), any such intellectual property and all embodiments of such intellectual property, provided the Noninvolved Party continues to fulfill its payment or royalty obligations as specified herein in full. Such intellectual property and all embodiments thereof shall be promptly delivered to the Noninvolved Party (a) upon any such commencement of a bankruptcy proceeding upon written request therefore by the Noninvolved Party, unless the Involved Party elects to continue to perform all of its obligations under this Agreement or (b) if not delivered under (a) above, upon the rejection of this Agreement by or on behalf of the Involved Party upon written request therefor by the Noninvolved Party. The foregoing is without prejudice to any rights the Noninvolved Party may have arising under the U.S. Bankruptcy Code or other applicable law.

9. Other Agreements. Concurrently with the execution of this Agreement, Isis and Pfizer shall enter into the Research Agreement. This Agreement and the Research Agreement are the sole agreements with respect to the subject matter and supersede all other agreements and understandings between the parties with respect to same.

10. Termination and Disengagement.

10.1 Unless sooner terminated in accordance with this Section 10, this Agreement will expire concurrently with the last to expire Royalty Payment Term.

10.2 **Events of Termination.** The following events shall constitute events of termination ("Events of Termination"):

(a) Any material written representation or warranty by Isis or Pfizer made under or in connection with this Agreement shall prove to have been incorrect in any material respect when made.

(b) Isis or Pfizer shall fail in any material respect to perform or observe any material term, covenant or understanding contained in this Agreement or the Research

Agreement, and any such failure shall remain un-remedied for thirty (30) days after written notice to the failing party.

(c) At any time, Pfizer may terminate this Agreement without cause upon **[***]** (**[***]**)**[***]**written notice to Isis.

10.3 Upon the occurrence of any Event of Termination described in Section 10.2(a) or 10.2(b), the party not responsible may, by written notice to the other party, terminate this Agreement.

10.4 Termination of this Agreement by either party, with or without cause, will not terminate the license granted pursuant to the first sentence of Section 5.2(a) or the license granted pursuant to Section 5.2(b) of the Research Agreement.

10.5 Termination of this Agreement for any reason shall be without prejudice to:

(a) the rights and obligations of the parties set forth in any sections which provide by their terms for performance by either party subsequent to termination;

(b) Isis' right to receive all royalty, milestone or other payments accrued hereunder; or

(c) any other remedies which either party may otherwise have.

11. Loss of Target Exclusivity.

11.1 Section 2.3 of the Research Agreement will terminate and be of no further force or effect upon the occurrence of the earliest of any the following events:

(a) Upon termination of the Research Agreement by Pfizer pursuant to Section 9.2(c) or 9.2(d) of the Research Agreement,

(b) Upon termination of the Research Agreement by Isis pursuant to Section 9.3(a) of the Research Agreement or Section 10.3 of this Agreement,

(c) Upon expiration of this Agreement,

(d) Upon termination of this Agreement by Pfizer pursuant to Section 10.2(c) of this Agreement.

11.2 Upon termination of Section 2.3 of the Research Agreement, Isis has the right to conduct research itself or sponsor any other research on the Exclusive Collaboration Gene Targets or engage in any research sponsored by any third party on the Exclusive Collaboration Gene Targets without

Pfizer's consent.

11.3 Pfizer may elect to designate any Exclusive Collaboration Gene Target as no longer subject to Section 2.3 of the Research Agreement by written notice to Isis. Such Exclusive Collaboration Gene Targets will no longer be subject to Section 2.3 of the Research Agreement upon the date of written notice by Pfizer.

12. Right of Reversion.

12.1 All Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products may transfer and revert to Isis and upon the assignment described in Section 12.3, all Program Technology and Program Know-how comprised of such pharmaceutical composition and/or use of ASOs and/or Products shall be deemed Isis Confidential Information, upon the earliest occurrence of any of the following events ("Reversion Trigger Events"):

(a) Upon termination of the Research Agreement by Pfizer pursuant to Section 9.2(c) or 9.2(d) of the Research Agreement,

(b) Upon termination of the Research Agreement by Isis pursuant to Section 9.3 (a) of the Research Agreement,

(c) Upon termination of this Agreement by Pfizer pursuant to Section 10.2(c) of this Agreement.

12.2 Isis must provide written notice to Pfizer within **[***]** (**[***]**) days of any Reversion Trigger Event to inform Pfizer of its election to exercise the right of reversion.

12.3 Upon receipt of written notice by Isis to exercise its right of reversion, Pfizer shall promptly assign all Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products to Isis and thereafter Isis will have the exclusive right, but not the obligation, to prepare, file, prosecute, maintain and/or defend such Patent Rights.

12.4 Upon Pfizer's assignment of any Patent Rights claiming the pharmaceutical composition and/or use of ASOs and/or Products to Isis and any transfer or reversion of Program Know-how to Isis, Isis will grant Pfizer and its agents a non-exclusive, non-transferable, irrevocable, worldwide, royalty-free, perpetual license, to make and use such Patent Rights and Program Know-how for all research purposes.

12.5 Upon receipt of Isis' election to exercise its right of reversion, Pfizer shall promptly make available to and transfer one copy or assign to Isis the following: **[***]**. Both parties shall have the right to use such information as they see fit in the research, development

and commercialization of products. **[***]**. Pfizer will also participate in a technical transfer meeting of no more than two days duration between the appropriate technical teams at Isis and Pfizer. Isis shall indemnify and hold Pfizer (and all officers, directors, employees, and agents of Pfizer) harmless for any and all damages, settlements, costs, legal fees and other expenses incurred in connection with a claim by a third party based on any action or omission of Isis, its agents, employees, or officers, related to or with regard to any use of such information or Isis' development and commercialization of Products. Pfizer shall have no liability whatsoever for any inaccuracy or incompleteness in such information.

12.6 **[***]**.

13. Indemnification. Pfizer and Isis will indemnify, defend and hold each other harmless for any and all damages, settlements, costs, legal fees and other expenses incurred in connection with a claim by a third party against either party based on any action or omission of the indemnifying party's agents, employees, or officers related to its obligations under this Agreement; provided, however, that the foregoing shall not apply (i) if the claim is found to be based upon the negligence, recklessness or wilful misconduct of the party seeking indemnification; or (ii) if such party fails to give the other party prompt notice of any claim it receives and such failure materially prejudices the other party with respect to any claim or action to which its obligation pursuant to this Section 13 applies. Notwithstanding the foregoing, Pfizer hereby expressly agrees to indemnify, defend and hold harmless Isis (and all officers, employees, consultants, directors, agents and Affiliates of Isis) for any and all claims arising from clinical trials pursued by Pfizer or its Affiliates or sublicensees, the sale of products, the exercise of rights granted to Pfizer under this Agreement or Section 5.2 of the Research Agreement (including without limitation product liability claims) and to claims arising from Patent Rights in Program Technology. The indemnifying party, in its sole discretion, shall choose legal counsel, shall control the defense of such claim or action and shall have the right to settle same on such terms and conditions it deems advisable; provided, however, that any settlement includes, as an unconditional term thereof, a full release of the indemnified party from all liability with respect to such claim. Pfizer and Isis at all times reserve the right to retain counsel of its own to defend their respective interests.

14. Notices and Reports.

14.1 All notices shall be deemed given as of the date received. All notices shall be made in writing, and mailed via certified mail, return receipt requested, courier, or facsimile transmission addressed as follows, or to such other address as may be designated from time to time:

If to Pfizer: Pfizer Global R&D Headquarters
50 Pequot Avenue
New London, CT 06320
Attn.: Executive Vice President, PGRD
with copy to: General Counsel, PGRD

Invoices should be sent to the following address:

[***]
[***]
[***]
[***]
[***]

If to Isis: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attn: Executive Vice President
With copy to: Vice-President, Legal

14.2 **Reports**. Pfizer agrees to keep Isis informed with respect to activities and progress toward further research, development and commercialization of Licensed Products. Pfizer agrees to provide to Isis every **[***]** a summary of such activities and progress. In addition, each party will immediately notify (and, if possible, provide as much advance notice as reasonably possible to) the other of any event such party deems to be material related to each Licensed Product (including any regulatory approval) so that the parties may analyze the need to or desirability of publicly disclosing or reporting such event.

15. Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of New York.

16. Miscellaneous.

16.1 **Binding Effect.** This Agreement shall be binding upon and inure to the benefit of the parties and their respective legal representatives, successors and permitted assigns.

16.2 **Headings.** Paragraph headings are inserted for convenience of reference only and do not form a part of this Agreement.

16.3 **Counterparts.** This Agreement may be executed simultaneously in two or more counterparts, each of which shall be deemed an original. Signatures may be transmitted via facsimile, thereby constituting the valid signature and delivery of this Agreement.

16.4 **Amendment; Waiver.** This Agreement may be amended, modified, superseded or cancelled, and any of the terms may be waived, only by a written instrument executed by each party or, in the case of waiver, by the party or parties waiving compliance. The delay or failure of any party at any time or times to require performance of any provisions shall in no manner affect the rights at a later time to enforce the same. No waiver by any party of any condition or of the breach of any term contained in this Agreement, whether by conduct, or otherwise, in any one or more instances, shall be deemed to be, or considered as, a further or continuing waiver of any such condition or of the breach of such term or any other term of this Agreement.

16.5 **No Third Party Beneficiaries.** No third party including any employee of any party to this Agreement, shall have or acquire any rights by reason of this Agreement. Nothing contained in this Agreement shall be deemed to constitute the parties as partners with each other or any third party.

16.6 **Assignment and Successors.** This Agreement may not be assigned by either party, except that each party may assign this Agreement and the rights and interests of such party, in whole or in part, to any of its Affiliates, any purchaser of all or substantially all of its assets or outstanding stock or to any successor company resulting from any merger or consolidation of such party with or into such corporation; provided however, that no Pfizer Confidential Information may be disclosed to any Isis acquirer or successor company as a result of a merger or consolidation involving Isis without Pfizer's prior written consent. Isis may assign its right to payment hereunder.

16.7 **Force Majeure.** Neither Pfizer nor Isis shall be liable for failure of or delay in performing obligations set forth in this Agreement, and neither shall be deemed in breach of its obligations, if such failure or delay is due to natural disasters or any causes reasonably beyond the control of Pfizer or Isis.

16.8 **Severability.** If any provision of this Agreement is or becomes invalid or is ruled invalid by any court of competent jurisdiction or is deemed unenforceable, it is the intention of the parties that the remainder of the Agreement shall not be affected so long as the essential benefits of this Agreement remains enforceable and obtainable.

16.9 **Survival of Terms.** In the event this Agreement expires or is terminated, certain terms that by their nature are intended to survive the expiration or termination of this Agreement shall survive and remain in full force until expiration or termination by their respective terms.

IN WITNESS WHEREOF, the parties have caused this Agreement to be executed by their duly authorized representatives.

Pfizer Inc **Isis Pharmaceuticals, Inc.**

By: /s/ John L. LaMattina

Title: President, PGRD

Date: 05/23/05

By: /s/ B. Lynne Parshall

Title: Executive Vice President & CFO

Date: 05/23/05

Exhibit I

RESEARCH PLAN
(Year 1)

[***]

Exhibit J

Contact: Claudine Prowse, Ph.D.
Isis Pharmaceuticals, Inc.
760-603-2331

ISIS PHARMACEUTICALS ANNOUNCES COLLABORATION WITH PFIZER TO DISCOVER ANTISENSE DRUGS FOR THE TREATMENT OF EYE DISEASE

CARLSBAD, CA, May 24, 2005 – Isis Pharmaceuticals Inc. (NASDAQ: ISIS) has entered into a multi-year drug discovery collaboration with Pfizer Inc (NYSE: PFE) to identify second-generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis will receive a technology access fee of $1 million, research funding, and milestone payments. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration.

Using Isis' proprietary second-generation antisense platform, the companies will work together to identify antisense drugs against targets selected by Pfizer. Pfizer will be responsible for clinical development and commercialization of the antisense drugs. Pfizer may develop the antisense drugs identified in the collaboration for all human health indications.

"Isis has already shown that antisense drugs can be effective in treating ocular diseases, having discovered and developed Vitravene®. We are excited to contribute to Pfizer's leading ophthalmology program and at the same time work with a recognized expert to extend the technology beyond our primary therapeutic focus," said C. Frank Bennett, Isis' Vice President of Antisense Research.

"This new collaboration reflects our active strategy to work with recognized leaders such as Pfizer to broaden and deepen our antisense pipeline moving forward. Because the antisense technology platform that Isis has pioneered allows us to very rapidly discover highly selective drugs to almost any gene target, we are able not only to keep our own pipeline full, but also provide drug candidates to partners," added Dr. Bennett.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. Through its Ibis division, Isis is developing a system to identify infectious organisms. As an innovator in RNA-based drug discovery and development,

Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at http://www.isispharm.com.

This press release includes forward-looking statements concerning Isis' collaboration with Pfizer Inc and the development, therapeutic potential and safety of antisense drugs in treating ophthalmic disease. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in Isis' Annual Report on Form 10-K for the year ended December 31, 2004, and quarterly report on Form 10-Q for the quarter ended March 30, 2005**,** which are on file with the U.S. Securities and Exchange Commission (SEC). Copies of these and other documents are available from the company.

VitraveneÒ is a registered trademark of Novartis AG

AGREEMENT FOR PURCHASE AND SALE

OF

2280 Faraday Avenue

San Diego, CA 92008

June 28, 2005

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AGREEMENT FOR PURCHASE AND SALE
OF
2280 FARADAY AVENUE, CARLSBAD, CA

THIS AGREEMENT FOR PURCHASE AND SALE is made and entered into as of June 28, 2005 (the "Effective Date") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation ("Seller"), and **ELECTRO SURFACE TECHNOLOGY, INC.,** a California corporation ("Buyer").

RECITALS

A. Seller owns certain improved real property situated at 2280 Faraday Avenue, Carlsbad, CA 92008, together with associated tangible and intangible personal property.

B. Buyer desires to purchase from Seller and Seller desires to sell to Buyer, subject to the terms and conditions contained in this Agreement, the foregoing real property and any and all associated tangible and intangible personal property owned by Seller.

AGREEMENT

NOW, THEREFORE, Buyer and Seller do hereby agree as follows:

ARTICLE I

BASIC DEFINITIONS

Closing Date. Unless otherwise agreed upon in writing by the Parties, the term "Closing Date" shall mean the 90th day following the Effective Date (i.e September 26, 2005), or any earlier date approved in writing by Buyer and Seller for the close of escrow with respect to the purchase and sale of the Property.

Contract Period. The term "Contract Period" shall mean the period from the date of this Agreement through and including the Closing Date.

Disclosure Statement. The term "Disclosure Statement" shall mean the statement set forth as **Exhibit A** to this Agreement.

Inspection Period. The term "Inspection Period" shall mean the period commencing on the Effective Date and ending at 5:00 p.m. California time on the 45th day following the Effective Date (i.e. August 12, 2005), *except* that solely with respect to the condition set forth in clause (iii) of Section 3.1(a), the Inspection Period will end at 5:00 p.m. California time on September 1, 2005. Notwithstanding the foregoing, if prior to September 1, 2005 (I) the appraisal in connection with Buyer's SBA loan has been completed; (II) the result of such appraisal is an amount sufficient to fund Buyer's SBA loan as contemplated by clause (iii) of Section 3.1(a); (III) Buyer's lenders' inform Seller that the lenders' are prepared to fund the SBA loan prior to the Closing Date, but subject to final loan committee approval; and (IV) one or both

of such loan committees have not met, but are scheduled to meet to approve Buyer's SBA loan on a date between September 1, 2005 and September 16, 2005, then with respect to the condition set forth in clause (iii) of Section 3.1(a), the Inspection Period will end at 12:00 p.m. California time on the first business day following the date such loan committees are scheduled to meet to approve Buyer's SBA loan.

Intangible Property. The term "Intangible Property" shall mean Seller's rights and interests in: (a) any and all transferable or assignable permits, building plans and specifications, certificates of occupancy, operating permits, sign permits, development rights and approvals, certificates, licenses, warranties and guarantees, trade names, service marks, engineering, soils, pest control and other reports relating to the Property, tenant lists, and advertising materials identified with the Property; (b) maintenance, service and other operating contracts, equipment leases and other arrangements or agreements to which Seller is a party affecting the ownership, repair, maintenance, management, leasing or operation of the Property; and (c) all other transferable intangible property, miscellaneous rights, benefits or privileges of any kind or character with respect to the Property.

Leases. The term "Leases" shall mean all leases, rental agreements or other agreements (including all amendments or modifications thereto) which entitle any person to the occupancy or use of any portion of the Property.

Personal Property. The term "Personal Property" shall mean all furniture, furnishings, trade fixtures, building systems and equipment (including, without limitation, HVAC, back-up generators, security and life safety systems) and other tangible personal property owned by Seller that is located at and used in connection with the operation of the Real Property.

Property. The term "Property" shall mean the Real Property, Seller's interest in the Leases, the Personal Property and the Intangible Property.

Real Property. The term "Real Property" shall mean that certain real property (including, without limitation, any and all other improvements thereon) situated at 2280 Faraday Avenue, Carlsbad, CA 92008. The land component of the Real Property is legally described in **Exhibit B** attached to this Agreement.

Title Company. The term "Title Company" shall mean First American Title Insurance Company, 411 Ivy Street, San Diego, CA 92101.

ARTICLE II

PURCHASE AND SALE

Section 2.1 Purchase and Sale. Seller agrees to sell the Property to Buyer, and Buyer agrees to purchase the Property upon all of the terms, covenants and conditions set forth in this Agreement.

Section 2.2 Purchase Price. The purchase price for the Property (the "Purchase Price") shall be the sum of $3,200,000.00. The entire amount of the Purchase Price (less the

Deposit delivered pursuant to Article V below) shall be payable by Buyer to Seller in cash on the Closing Date through the escrow described in Section 6.1 below.

Section 2.3 Buyer's Review and Seller's Disclaimer.

(a) Subject to the provisions of subsection 2.3(c) below, during the Inspection Period Buyer shall be permitted to make a complete review and inspection of the physical, legal, economic and environmental condition of the Property, including, without limitation, any leases and contracts affecting the Real Property, books and records maintained by Seller or its agents relating to the Property, boundary and other survey-related issues relating to the Real Property, pest control matters, soil condition, asbestos, PCB, hazardous waste, toxic substance or other environmental matters, compliance with building, health, safety, land use and zoning laws, regulations and orders, plans and specifications, structural, life safety, HVAC and other building system and engineering characteristics, traffic patterns and all other information pertaining to the Property. Without representation or warranty, Seller shall cooperate in Buyer's review and provide Buyer with the opportunity to review leases, financial reports, survey and other third party inspection reports and similar non-proprietary or non-confidential materials in Seller's possession relating to the Property. Buyer acknowledges (i) that Buyer has entered into this Agreement with the intention of making and relying upon its own investigation of the physical, environmental, economic and legal condition of the Property, and (ii) that Buyer is not relying upon any representations and warranties, other than those specifically set forth in Section 4.1 below, made by Seller or anyone acting or claiming to act on Seller's behalf concerning the Property. Buyer further acknowledges that it has not received from Seller any accounting, tax, legal, architectural, engineering, property management or other advice with respect to this transaction and is relying solely upon the advice of its own accounting, tax, legal, architectural, engineering, property management and other advisors. Buyer specifically undertakes and assumes all risks associated with the matters disclosed by Seller on the Disclosure Statement. Subject to the provisions of Section 4.1 of this Agreement, Buyer shall purchase the Property in its "as is" condition on the Closing Date and assumes the risk that adverse physical, environmental, economic or legal conditions may not have been revealed by its investigation. Furthermore, at Seller's expense, Seller will engage Kleinfelder Inc, or such other environmental consulting firm as reasonably approved by Buyer, to analyze a single core sample taken from the sump area located on the Property using the analytical methods listed on Schedule 2.3(a) attached hereto, with the results of such analysis to be provided electronically (the "Core Test"). Seller will provide the results of such Core Test to Buyer on or before 5:00 p.m. on the 25th day following the Effective Date.

(b) Except with respect to any claims arising out of any breach of covenants, representations or warranties set forth in Section 4.1 below, Buyer, for itself and its agents, affiliates, successors and assigns, hereby releases and forever discharges Seller, its agents, affiliates, successors and assigns from any and all rights, claims and demands at law or in equity, whether known or unknown at the time of this agreement, which Buyer has or may have in the future, arising out of the physical, environmental, economic or legal condition of the Property, including, without limitation, any claim for indemnification or contribution arising under the Comprehensive Environmental Response, Compensation and Liability Act (42 U.S.C. Section 9601, et. seq.) or any similar federal, state or local statute, rule or ordinance relating to liability of property owners for environmental matters. For the foregoing purposes, Buyer hereby

specifically waives the provisions of Section 1542 of the California Civil Code and any similar law of any other state, territory or jurisdiction. Section 1542 provides:

> 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.

Buyer hereby specifically acknowledges that Buyer has carefully reviewed this subsection and discussed its import with legal counsel and that the provisions of this subsection are a material part of this Agreement.

_____
Buyer

By proceeding with the close of escrow, Buyer shall be deemed for all purposes to have remade as of the Closing Date, all of the statements set forth in this Section 2.3(b).

(c) Buyer's exercise of the rights of review and inspection set forth in subsection (a) shall be subject to the following limitations: (i) any entry onto the Real Property by Buyer, its agents or representatives, shall be during normal business hours, following reasonable prior notice to Seller and delivery to Seller of satisfactory evidence of Buyer's general liability insurance (in the amount of at least $1,000,000 per occurrence, $3,000,000 aggregate, and with Seller named as an additional insured), and, at Seller's discretion, accompanied by a representative of Seller; (ii) Buyer shall not conduct any drilling, test borings or other disturbance of the Real Property for review of soils, compaction, environmental, structural or other conditions without Seller's prior written consent; (iii) Buyer shall exercise reasonable diligence not to disturb the use or occupancy of any occupant of the Property; and (iv) Buyer shall indemnify, defend and hold Seller harmless from all loss, cost, and expense resulting from any entry or inspections performed by Buyer, its agents or representatives.

Section 2.4 Permitted Title Exceptions. During the Inspection Period, Seller with provide to Buyer from Title Company and Buyer will review a preliminary title report with respect to the Real Property, together with all documents and information pertaining to the exceptions to title listed in such report. In addition, Buyer shall, at its expense, obtain during the Inspection Period any survey of the Real Property desired by Buyer or required by Title Company as a condition to the issuance of the Title Policy described in Section 3.1(a)(ii) below (the "Survey"). Buyer may advise Seller in writing and in reasonable detail, not later than five (5) business days prior to the close of the Inspection Period, what exceptions to title, if any, listed in the then current preliminary report or disclosed on the Survey are not acceptable to Buyer (the "Title Objections"). Buyer shall not, however, unreasonably express disapproval of any exceptions to title and, prior to notifying Seller of any Title Objections, shall endeavor in good faith to cause Title Company to modify and update the preliminary report to reflect requested corrections and revisions. Seller shall have five (5) business days after receipt of Buyer's Title Objections to give Buyer notice that (a) Seller will remove any Title Objections from title (or afford the Title Company necessary information or certifications to permit it to insure over such exceptions) or (b) Seller elects not to cause such exceptions to be removed. Seller's failure to

provide notice to Buyer within such five (5) business day period as to any Title Objection shall be deemed an election by Seller not to remove the Title Objection. If Seller so notifies or is deemed (pursuant o the previous sentence) to have notified Buyer that Seller shall not remove any or all of the Title Objections, Buyer shall have until the close of the Inspection Period to determine whether (i) to proceed with the purchase and take the Property subject to

such exceptions or (ii) to terminate this Agreement, in which case the Deposit made by Buyer to Title Company will promptly be returned to Buyer in its entirety. "Permitted Exceptions" shall include and refer to any and all exceptions to title, excepting solely Title Objections that have been timely identified by Buyer and that Seller has notified Buyer pursuant to this Section that Seller is willing to remove.

ARTICLE III

CONDITIONS PRECEDENT

Section 3.1 Conditions.

(a) Notwithstanding anything in this Agreement to the contrary, Buyer's obligation to purchase the Property shall be subject to and contingent upon the satisfaction or waiver of the following conditions precedent:

(i) Buyer's inspection and approval, within the Inspection Period, of all physical, environmental (including, but not limited to the Core Test), economic and legal matters relating to the Property, pursuant to Section 2.3 above;

(ii) The willingness of Title Company to issue, upon the sole condition of the payment of its regularly scheduled premium, its American Land Title Association extended coverage Owner's Policy of Title Insurance 1992 Form (the "Title Policy"), with such endorsements as may have been requested by Buyer and agreed to by Title Company during the Inspection Period, insuring Buyer in the amount of the Purchase Price that title to the Real Property is vested of record in Buyer on the Closing Date subject only to the printed conditions and exceptions of such policy and the Permitted Exceptions;

(iii) Prior to the expiration of the Inspection Period, Buyer obtaining a commitment for an SBA loan for a sum equal to at least 90% of the Purchase Price; *provided, however*, from and after the expiry of the Inspection Period, the condition set forth in this clause (iii) will be null and void;

(iv) Seller's performance or tender of performance of all material obligations under this Agreement and the material truth and accuracy of Seller's express representations and warranties.

(b) Notwithstanding anything in this Agreement to the contrary, Seller's obligation to sell the Property shall be subject to and contingent upon the satisfaction or waiver of the following conditions precedent:

(i) Buyer's performance or tender of performance of all material obligations under this Agreement and the material truth and accuracy of Buyer's express representations and warranties;

(ii) The board of directors of Buyer will have approved the sale of the Property pursuant to the terms of this Agreement; *provided, however* that this condition (ii) will become null and void after the expiration of the Inspection Period; and

(iii) The satisfaction of the conditions set forth in subparagraphs (a)(i) through (iii) above.

Section 3.2 Failure or Waiver of Conditions Precedent. In the event any of the conditions set forth in Section 3.1 are not fulfilled or waived, the party benefited by such condition may, by written notice to the other party, terminate this Agreement, whereupon all rights and obligations hereunder of each party shall be at an end. Either party may, at its election, at any time or times on or before the date specified for the satisfaction of the condition, waive in writing the benefit of any of the conditions set forth in Section 3.1(a) and 3.1(b) above. Notwithstanding any contrary provision of this Agreement, Buyer shall be deemed to have completed the inspection and approval described in Section 3.1(a)(i) above, and the condition set forth in that clause shall be deemed satisfied, unless Buyer delivers to Seller written notice of failure of such condition on or prior to the close of the Inspection Period. In the event this Agreement is terminated as a result of the failure of any condition set forth in Section 3.1(a), Seller shall return the full amount of the Deposit to Buyer. In any event, Buyer's consent to the close of escrow pursuant to this Agreement shall waive any remaining unfulfilled conditions.

ARTICLE IV

COVENANTS, WARRANTIES AND REPRESENTATIONS

Section 4.1 Seller's Warranties and Representations. Seller hereby makes the following representations and warranties to Buyer as of the date of this Agreement; provided that each of such representations and warranties shall be deemed to be modified by any contrary or qualifying information contained in any reports, schedules or other informational materials delivered or made available to Buyer pursuant to this Agreement or set forth on the Disclosure Statement:

(a) Seller has full power and lawful authority to enter into and carry out the terms and provisions of this Agreement and to execute and deliver all documents which are contemplated by this Agreement, and all actions of Seller necessary to confer such power and authority upon the persons executing this Agreement (and all documents which are contemplated by this Agreement) on behalf of Seller have been taken;

(b) To Seller's knowledge, (i) the list of service and equipment contracts attached to this Agreement as **Exhibit D** is a complete and accurate list of all of the service and equipment contracts presently in effect with respect to the Real Property, (ii) the copies of such contracts that have been (or will be) delivered or made available to Buyer are true, correct and complete, and (iii) each such contract is in full force and effect;

(c) To Seller's knowledge, Seller has received no written notice from any governmental authorities that (i) eminent domain proceedings for the condemnation of the Real Property are pending or (ii) that the Property or its operation violates in any way any applicable laws, ordinances, rules, regulations, judgments, orders, covenants, conditions or restrictions, whether federal, state, local, foreign or private, including without limitation the Americans with Disabilities Act and applicable environmental laws, rules and regulations, the violation of which would result in a material adverse change in the Property or its operation;

(d) To Seller's knowledge, Seller has received no written notice of any threatened or pending litigation against Seller or affecting the Real Property which would materially and adversely affect the Real Property or Seller's capacity to perform under this Agreement;

(e) Seller is not a "foreign person" within the meaning of Section 1445(f)(3) of the Internal Revenue Code; and

(f) To Seller's knowledge, Seller has received no written notice from any governmental authority that any of the improvements located on the Real Property are presently in violation of any applicable building codes, zoning or land use laws, or other law, order, ordinance, rule or regulation affecting the Real Property.

As used herein, the term "Seller's knowledge" or words of similar effect shall mean the current actual, subjective knowledge of (i) Patricia Lowenstam, Vice President Human Resources, Operations, Health, Safety and Environment, (ii) Elizabeth Hougen, Vice President Finance and (iii) Grantland E. Bryce, Vice President Legal and General Counsel. Neither Patricia Lowenstam, Elizabeth Hougen or Grantland Bryce nor any party other than Seller shall bear responsibility for any breach of representation. Notwithstanding the foregoing, an officer of Isis identified above charged with responsibility for the aspect of the business relevant or related to the matter at issue will be deemed to have knowledge of a particular matter if, in the reasonable exercise of his or her duties and responsibilities, such officer should have known of such matter.

Section 4.2 **Seller's Covenants**. Seller hereby covenants and agrees as follows:

(a) during the Contract Period, Seller shall ensure that the Property is operated and maintained in a manner consistent with current practices and maintain reasonable and customary levels and coverages of insurance and Seller shall not create or acquiesce in the creation of liens or exceptions to title other than the Permitted Exceptions or voluntarily take any action (other than as may be permitted pursuant to subparagraphs (b) and (c) of this Section 4.2) to render any of the representations or warranties of Seller set forth in Section 4.1 materially incorrect; and

(b) during the Contract Period, Seller will not execute or modify any Leases or other contracts, (i) without promptly notifying Buyer thereof and providing Buyer with copies of the relevant contract documents, and (ii) as to any Lease or other contract (or modification thereof) executed during the period between the expiration of the Inspection Period and the Closing Date, without Buyer's prior approval, which approval shall not be unreasonably

withheld and shall be deemed given if Buyer should fail to approve or disapprove any such matter in writing within 5 days following Seller's request for such action.

(c) Notwithstanding anything to the contrary contained in this Section 4.2, Seller is permitted to grant Electronic Online Systems International ("EOS") a non-exclusive easement to the parking spaces depicted on Schedule 4.2(c), solely in connection with the sale of the property located at 2292 Faraday Avenue, Carlsbad, CA 92008 ("2292 Faraday"); *provided, however*, that if Seller does not ultimately sell 2292 Faraday to EOS, this exception to Section 4.2 will become null and void.

Section 4.3 **Buyer's Warranties and Representations**. Buyer hereby represents and warrants to Seller that (a) Buyer has and as of the Closing Date shall have, full power and lawful authority to enter into and carry out the terms and conditions of this Agreement and to execute and deliver all documents which are contemplated by this Agreement, (b) all actions necessary to confer such power and authority upon the persons executing this Agreement and all documents which are contemplated by this Agreement to be executed on behalf of Buyer or its assignee have been taken, (c) Buyer has received no written notice of any threatened or pending litigation which would materially and adversely affect Buyer's capacity to perform under this Agreement, (d) Buyer has received a SBA approval letter from a reputable financial institution in an amount that will allow Buyer to satisfy its obligation to pay the Purchase Price; and (e) Buyer believes that, unless matters having a material adverse economic effect on the Property are discovered by Buyer during the Inspection Period, the Purchase Price as set forth in Section 2.2 above is a fair and reasonable price to pay for the Property. Buyer warrants and represents to Seller that Buyer will not attempt to renegotiate the Purchase Price unless such matters having a material adverse economic effect on the Property are discovered by Buyer during the Inspection Period.

Section 4.4 **Limitations**.

(a) The parties agree that (i) Seller's warranties and representations contained in this Agreement and in any document executed by Seller pursuant to this Agreement shall survive Buyer's purchase of the Property only for a period of 180 days after the Closing Date (the "Limitation Period"), (ii) Seller's aggregate liability for claims arising out of such representations and warranties shall not exceed $500,000.00 and (iii) Buyer shall provide actual written notice to Seller of any breach of such warranties or representations and shall allow Seller 30 days within which to cure such breach, or, if such breach cannot reasonably be cured within 30 days, an additional reasonable time period, so long as such cure has been commenced within such 30 days and diligently pursued. If Seller fails to cure such breach after actual written notice and within such cure period, Buyer's sole remedy shall be an action at law for damages as a consequence thereof, which must be commenced, if at all, within the Limitation Period; provided, however, that if within the Limitation Period Buyer gives Seller written notice of such a breach and Seller commences to cure and thereafter terminates such cure effort, Buyer shall have an additional 30 days from the date of such termination within which to commence an action at law for damages as a consequence of Seller's failure to cure. The Limitation Period referred to herein shall apply to known as well as unknown breaches of such warranties or representations.

(b) Notwithstanding any contrary provision of this Agreement, if Seller becomes aware during the Contract Period of any matters which make any of its representations or warranties untrue, Seller shall promptly disclose such matters to Buyer in writing. In the event that Seller so

discloses any matters which make any of Seller's representations or warranties untrue in any material respect or in the event that Buyer otherwise becomes aware during the Contract Period of any matters which make any of Seller's representations or warranties untrue in any material respect, Seller shall bear no liability for such matters (provided that Seller has not breached an express covenant set forth in this Agreement), but Buyer shall have the right to elect in writing on or before the Closing Date, (i) to waive such matters and complete the purchase of the Property in accordance with the terms of this Agreement, or (ii) as to any matters disclosed following the expiration of the Inspection Period, to terminate this Agreement and receive a refund of the Deposit and any earnings thereon, plus reimbursement from Seller for Buyer's reasonable out of pocket costs incurred in connection with the negotiation of this Agreement, Buyer's diligence with respect to the Property, and Buyer's actions in furtherance of the transactions contemplated by this Agreement (provided that said sum recoverable as reimbursement shall not exceed $25,000). Buyer's delivery of the Additional Deposit shall constitute Buyer's conclusive agreement to accept or waive any such matters disclosed to Buyer prior to the close of the Inspection Period.

Section 4.5 **Indemnifications**. Subject to the foregoing limitations and the provisions of Sections 6.3, 6.4 and 7.12:

(a) Seller shall indemnify and defend Buyer against and hold Buyer harmless from any and all claims, liabilities, losses, damage, costs and expenses, including, without limitation, all reasonable attorneys' fees, asserted against or suffered by Buyer resulting from (i) any breach by Seller of this Agreement, and (ii) the untruth, inaccuracy or breach of any of the representations and warranties made by Seller pursuant to this Agreement.

(b) Buyer shall indemnify and defend Seller against and hold Seller harmless from any claim, loss, damage, or expense, including any reasonable attorneys fees, asserted against or suffered by Seller resulting from (i) any breach by Buyer of this Agreement, (ii) the untruth, inaccuracy or breach of any of the representations or warranties made by Buyer pursuant to this Agreement, and (iii) any liability or obligation arising in connection with the Property accruing following the Closing Date.

ARTICLE V

DEPOSIT

Within 5 business days following the mutual execution of this Agreement by Buyer and Seller, Buyer shall deliver to Title Company, for deposit into such escrow, the sum of $50,000.00 (the "Initial Deposit"). On or before the expiration of the Inspection Period, Buyer shall deliver to Title Company the additional sum of $150,000.00 (the "Additional Deposit"), which, together with the Initial Deposit, shall be referred to in this Agreement as the "Deposit". In the event that this transaction is consummated as contemplated by this Agreement, then the entire amount of the Deposit, together with any interest accrued thereon, shall be credited against the Purchase Price. The entire amount of the Deposit, together with any interest accrued thereon, shall be

returned immediately to Buyer in the event of the failure of any of the conditions precedent set forth in Section 3.1(a) above or in the event that (a) the conditions precedent set forth in Section 2.4 or 3.1(b) shall have been satisfied or waived, (b) Buyer shall have performed fully or tendered performance of its obligations hereunder and (c) Seller shall be unable or fail to perform its obligations, under this Agreement. IN ALL OTHER EVENTS, THE ENTIRE AMOUNT OF THE DEPOSIT, PLUS ACCRUED INTEREST, SHALL BE RETAINED BY SELLER AS LIQUIDATED DAMAGES. BUYER AND SELLER HEREBY ACKNOWLEDGE AND AGREE THAT SELLER'S DAMAGES IN THE EVENT OF SUCH A BREACH OF THIS AGREEMENT BY BUYER WOULD BE DIFFICULT OR IMPOSSIBLE TO DETERMINE, THAT THE AMOUNT OF THE DEPOSIT PLUS ACCRUED INTEREST IS THE PARTIES' BEST AND MOST ACCURATE ESTIMATE OF THE DAMAGES SELLER WOULD SUFFER IN THE EVENT THE TRANSACTION PROVIDED FOR IN THIS AGREEMENT FAILS TO CLOSE, AND THAT SUCH ESTIMATE IS REASONABLE UNDER THE CIRCUMSTANCES EXISTING ON THE DATE OF THIS AGREEMENT. BUYER AND SELLER AGREE THAT SELLER'S RIGHT TO RETAIN THE DEPOSIT PLUS ACCRUED INTEREST SHALL BE THE SOLE REMEDY OF SELLER AT LAW IN THE EVENT OF SUCH A BREACH OF THIS AGREEMENT BY BUYER. THE FOREGOING, HOWEVER, IS A LIQUIDATED MEASURE OF DAMAGES FOR THE SPECIFIED BREACH ONLY, AND SHALL NOT LIMIT BUYER'S LIABILITY UNDER SECTIONS 2.3, 4.5 OR 7.9 OF THIS AGREEMENT.

ACCEPTED AND AGREED TO:

Seller	Buyer

ARTICLE VI

ESCROW AND CLOSING

Section 6.1 **Escrow Arrangements**. An escrow for the purchase and sale contemplated by this Agreement has been opened by Buyer and Seller with Title Company. On or before the Closing Date, Seller and Buyer shall each deliver escrow instructions to Title Company consistent with this Article VI, and the parties shall deposit in escrow the funds and documents described below.

(a) Seller shall deposit (or cause to be deposited):

(i) a duly executed and acknowledged grant deed in favor of Buyer from Seller with respect to the Real Property in the form attached to this Agreement as **Exhibit E** (the "Deed");

(ii) a duly executed bill of sale with respect to the Personal Property in the form attached to this Agreement as **Exhibit F** (the "Bill of Sale");

(iii) a duly executed counterpart of an assignment and assumption of Seller's interest in the Intangible Property in the form attached to this Agreement as **Exhibit G** (the "Assignment of Intangible Property");

(iv) a certificate from Seller certifying the information required by §§ 18662 of the California Revenue and Taxation Code and the regulations issued thereunder to establish that the transaction contemplated by this Agreement is exempt from the tax withholding requirements of such provisions (the "California Certificate"); and

(v) a certificate from Seller certifying the information required by §1445 of the Internal Revenue Code and the regulations issued thereunder to establish, for the purposes of avoiding Buyer's tax withholding obligations, that Seller is not a "foreign person" as defined in Internal Revenue Code § 1445(f)(3) (the "FIRPTA Certificate"); and

(b) Buyer shall deposit:

(i) immediately available funds sufficient to pay the balance of the Purchase Price, plus sufficient additional cash to pay Buyer's share of all escrow costs and closing expenses;

(ii) a duly executed counterpart of the Assignment of Intangible Property; and

(iii) a certificate duly executed by Buyer in favor of Seller confirming the waivers and acknowledgments set forth in Sections 2.3(a) and (b) above.

Section 6.2 **Closing**. Title Company shall close escrow by:

(a) recording the Deed;

(b) causing Title Company to issue the Title Policy to Buyer;

(c) delivering to Buyer the Bill of Sale, the FIRPTA Certificate, the California Certificate and the counterpart Assignment of Intangible Property executed by Seller; and

(d) delivering to Seller the counterpart Assignment of Intangible Property executed by Buyer and the certificate described in Section 6.1(b)(iv) above, and funds in the amount of the Purchase Price, as adjusted for credits, prorations and closing costs in accordance with this Article VI.

Section 6.3 **Prorations**.

(a) Real estate taxes and assessments constituting a lien and allocable to the payment period that includes the Closing Date, personal property taxes, if any, rental income and all other items of income and expense with respect to the Property shall be prorated between Seller and Buyer as of the Closing Date. Income and expenses shall be prorated on the basis of a 30-day month and on the basis of the accrual method of accounting. All such items attributable to the period through and including the Closing Date shall be credited to Seller; all such items

attributable to the period following the Closing Date shall be credited to Buyer. Buyer shall be credited in escrow with (i) any portion of rental agreement or lease deposits in Seller's possession with respect to the Property which are refundable to the tenants and (ii) rent prepaid beyond the Closing Date. Buyer shall not be entitled to any interest on rental agreement or lease deposits or prepaid rent accrued on or before the Closing Date. Seller shall be credited in escrow with any refundable deposits or bonds held by any utility, governmental agency or service contractor with respect to the Property. Seller shall also be credited in escrow with any prepaid real estate taxes and assessments allocable to the period after the Closing Date. In addition, Seller shall be credited in escrow with any leasing commissions, free rental periods or tenant improvement or other allowances paid or incurred by Seller during the Contract Period to the extent such amounts (x) were disclosed in the copies of the Leases delivered to Buyer or were otherwise disclosed to Buyer during the Inspection Period, and (y) are equitably allocable to that portion of the stabilized term (i.e., the term following the tenant's entry into occupancy and commencement of unabated rental obligations) of any new or existing Lease of the Property following the Closing Date. To the extent disclosed to Buyer by Seller, Buyer shall assume all obligations for any such leasing commissions, free rental periods or tenant improvement or other allowances payable following the Closing Date.

(b) Buyer and Seller shall cooperate to produce prior to the Closing Date a schedule of prorations to be made on and after the Closing Date as complete and accurate as reasonably possible. With respect to taxes or other expenses payable or reimbursable by the tenants of the Property, the amounts prorated between Buyer and Seller shall be the net amounts (if any) not subject to payment or reimbursement by the tenants. All prorations which can be liquidated accurately or reasonably estimated as of the Closing Date shall be made in escrow on the Closing Date. All other prorations, and adjustments to initial estimated prorations, shall be made by the parties with due diligence and cooperation within 30 days following the Closing Date, or such later time as may be required to obtain necessary information for proration, by immediate cash payment to the party yielding a net credit from such prorations from the other party.

Section 6.4 **Other Closing Costs**.

(a) Seller shall pay (i) any county documentary transfer or transaction taxes or fees due on the transfer of the Property, (ii) fifty percent (50%) of any city documentary transfer or transaction taxes or fees due on the transfer of the Property, (iii) fifty percent (50%) of all escrow, recording or other fees or costs charged by or reimbursable to Title Company, (iv) the CLTA portion of the title insurance premium for the Title Policy (but only for a liability amount equal to the Purchase Price), (v) all fees and expenses of its legal counsel and other third party consultants engaged by or on behalf of Seller in connection with this transaction and (vi) any prepayment fees or penalties, if any, to pay off existing mortgages affecting the Property.

(b) Buyer shall pay (i) balance of the premium for the Title Policy (including costs of endorsements, extended coverage and related survey costs), (ii) fifty percent (50%) of all escrow, recording or other fees or costs charged by or reimbursable to Title Company, (iii) any sales or use taxes determined to be payable in connection with this transaction, (iv) fifty percent (50%) of any city documentary transfer or transaction taxes or fees due on the transfer of the Property, (v) the cost of the Survey, (vi) all fees and expenses of its legal counsel and other third

party consultants engaged by or on behalf of Buyer in connection with this transaction, and (vi) the balance of the premium for the Title Policy (including costs of endorsements, extended coverage and related survey costs.

(c) Any costs and expenses of closing that are not expressly identified in subparagraph (a) or (b) above shall be allocated between the parties in accordance with prevailing custom in San Diego County.

Section 6.5 **Further Documentation**. At or following the close of escrow, Buyer and Seller each shall execute any certificate or other instruments required by law or local custom or otherwise reasonably requested by the other party to effect the transaction contemplated by this Agreement.

ARTICLE VII

MISCELLANEOUS

Section 7.1 **Damage or Destruction**.

(a) Buyer shall be bound to purchase the Property for the Purchase Price as required by the terms of this Agreement without regard to the occurrence or effect of any damage to or destruction of the improvements on the Real Property or condemnation by right of eminent domain, provided that the occurrence of any damage or destruction is (i) covered by insurance (excepting deductibles), or (ii) if not covered by insurance, involves repair costs of $250,000 or less. If Buyer is so bound to purchase notwithstanding the occurrence of damage, destruction or condemnation, upon the close of escrow: (A) in the event of damage covered by insurance, Buyer shall receive a credit against the Purchase Price in the amount (net of collection costs) of any insurance proceeds or condemnation award collected and retained by Seller as a result of any such damage or destruction or condemnation and Seller shall assign to Buyer all rights to such insurance proceeds or condemnation awards as shall not have been collected prior to the close of escrow; and (B) in the event of damage not covered by insurance, Buyer shall receive a credit (not to exceed $250,000) in the amount of the estimated cost to repair the damage.

(b) Buyer or Seller may terminate this Agreement by written notice of election given promptly to the other party following the event if there occurs damage or destruction not covered by insurance which involves repair costs in excess of $250,000.

Section 7.2 **Brokerage Commissions and Finder's Fees**. Except for Lannie R. Allee of CB Richard Ellis and Kent Moore of Grubb & Ellis/BRE, each party to this Agreement warrants to the other that no person or entity can properly claim a right to a real estate commission, real estate finder's fee, real estate acquisition fee or other real estate brokerage-type compensation (collectively, "Real Estate Compensation") based upon the acts of that party with respect to the transaction contemplated by this Agreement. Each party hereby agrees to indemnify and defend the other against and to hold the other harmless from any and all loss, cost, liability or expense (including but not limited to attorneys' fees and returned commissions) resulting from any claim for Real Estate Compensation by any person or entity based upon such

acts. Seller will be responsible for paying any Real Estate Compensation to CB Richard Ellis and Grub & Ellis per separate agreement.

Section 7.3 **Successors and Assigns**. Buyer may not assign any of Buyer's rights or duties hereunder without the prior written consent of Seller, which consent will not be unreasonably withheld; provided that Buyer may assign this Agreement (a) to an entity affiliated with Buyer which has, in Seller's reasonable judgment, the financial capacity to perform the obligations of Buyer hereunder, or (b) to an entity directly or indirectly owned by the principals of Buyer, which is controlled by the principals of Buyer. No assignment by Buyer shall relieve Buyer of its obligations under this Agreement. Subject to the limitations on assignment expressed in this Section 7.3, this Agreement shall be binding upon, and inure to the benefit of, Buyer and Seller and their respective successors and assigns.

Section 7.4 **Notices**. All notices or other communications required or provided to be sent by either party shall be in writing and shall be sent by United States Postal Service, postage prepaid or certified mail, return receipt requested, by any nationally known overnight delivery service, by courier, or in person. All notices shall be deemed to have been given forty-eight (48) hours following deposit in the United States Postal Service or upon personal delivery if sent by overnight delivery service, courier or personally delivered. All notices shall be addressed to the party at the address below:

To Seller:
Patricia Lowenstam
VP Human Resources and Operations
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

with a copy to:
General Counsel
Fax: 760-268-4922

To Buyer:

Attn:

and with a copy to:
The Roth Law Firm
A Professional Law Corporation
11770 Bernardo Plaza Court
Suite 315
San Diego, CA 92128
Fax: 858-451-3643

Any address or name specified above may be changed by notice given to the addressee by the other party in accordance with this Section 7.4. The inability to deliver because of a changed

address of which no notice was given, or rejection or other refusal to accept any notice, shall be deemed to be the receipt of the notice as of the date of such inability to deliver or rejection or refusal to accept. Any notice to be given by any party hereto may be given by the counsel for such party.

Section 7.5 **Time**. Time is of the essence of every provision contained in this Agreement.

Section 7.6 **Possession**. The rights of possession of the Property (subject to the Leases) shall be delivered to Buyer on the Closing Date.

Section 7.7 **Incorporation by Reference**. All of the exhibits attached to this Agreement or referred to herein and all documents in the nature of such exhibits, when executed, are by this reference incorporated in and made a part of this Agreement.

Section 7.8 **No Deductions or Off-Sets**. Buyer acknowledges that the Purchase Price to be paid for the Property pursuant to this Agreement is a net amount and shall not be subject to any off-sets or deductions.

Section 7.9 **Attorneys' Fees**. In the event any dispute between Buyer and Seller should result in litigation, the prevailing party shall be reimbursed for all reasonable costs incurred in connection with such litigation, including, without limitation, reasonable attorneys' fees.

Section 7.10 **Construction**. The parties acknowledge that each party and its counsel have reviewed and revised this Agreement and that the normal rule of construction to the effect that any ambiguities are to be resolved against the drafting party shall not be employed in the interpretation of this Agreement or any amendments or exhibits hereto.

Section 7.11 **Governing Law**. This Agreement shall be construed and interpreted in accordance with and shall be governed and enforced in all respects according to the laws of the State of California.

Section 7.12 **Damages**. Buyer agrees that any liability of Seller under any claim brought prior to the Closing Date pursuant to this Agreement or any document or instrument delivered simultaneously or in connection with, or pursuant to this Agreement, shall be limited solely to its interest in the Property, and no other assets of Seller shall be subject to levy or execution. With respect to any such claim brought following the Closing Date, any liability of Seller shall be limited to Seller's assets and to the amount set forth in clause (ii) of Section 4.4 above. In no event shall Buyer seek satisfaction for any such obligation from any of Seller's members or from any members, shareholders, officers, directors, trustees, beneficiaries, employees, agents, legal representatives, successors or assigns of such members, nor shall any such person or entity have any personal liability for any such obligations of Seller.

Section 7.13 **Confidentiality**. Each Party hereby acknowledges and agrees that the existence of this Agreement, and the terms and conditions set forth herein, are to be kept strictly confidential. Accordingly, except as may be required by law or court order, each Party shall not,

without the prior written consent of the other Party, release, publish or otherwise distribute (and shall not authorize or permit any other person or entity to release, publish or otherwise distribute) any information concerning this Agreement or the transaction contemplated herein to any person or entity other than Buyer's prospective lenders and each Party's respective legal and financial advisors, each of whom shall agree to hold such information strictly confidential as if such persons were bound by the provisions of this Section 7.13. The obligations of this Section 7.13 will not apply to information that the receiving party can establish by written records (a) was known by it prior to the receipt of the confidential information from the disclosing Party; (b) was disclosed to the receiving Party by a third party having the right to do so; (c) was, or subsequently became, in the public domain through no fault of the receiving Party, its officers, directors, employees or agents; (d) was disclosed on a confidential basis to such Party's accountants, attorneys and other professional advisors in connection with the transactions contemplated by this Agreement; or (e) was disclosed by the receiving Party pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as the receiving party provides the disclosing party with sufficient prior notice in order to allow the disclosing party to contest such request, requirement or order

Section 7.14 **Counterparts**. This Agreement may be executed in one or more counterparts. All counterparts so executed shall constitute one contract, binding on all parties, even though all parties are not signatory to the same counterpart.

Section 7.15 **Tax Deferred Exchange.** Upon the request of either party (the "Requesting Party") to this Agreement, the other party (the "Non-Requesting Party") at no cost or expense to the Non-Requesting Party agrees to reasonably cooperate with the Requesting Party in consummating the sale of the Property as part of a simultaneous or non-simultaneous tax-deferred exchange (the "Exchange") pursuant to Section 1031 of the Internal Revenue Code of 1986, as amended, *provided* that (i) the Non-Requesting Party shall not be required to take title to any property other than the Property, and (ii) the Closing Date shall not be delayed or extended thereby. The Requesting Party shall have the right to assign its rights and obligations hereunder to an accommodation entity (the "Intermediary"), who will cause the Closing to occur on the Requesting Party's behalf. All of the Requesting Party's liabilities, representations and warranties under this Agreement shall remain those of the Requesting Party and the Non-Requesting Party shall not seek recourse against the Intermediary with respect to such liabilities or for the breach of any such representations or warranties. Performance by an Intermediary in effectuating an exchange will be treated as if such performance were made by the Requesting Party, and the Requesting Party shall remain the primary obligor for the full and timely performance of all obligations of the Requesting Party under this Agreement. In the event of any breach of such representations, warranties, covenants, or other obligations, the Non-Requesting Party shall proceed directly against the Requesting Party. The Non-Requesting Party shall not be required to assume any liabilities as a result of the exchange transaction that are in addition to those which would exist if the transaction were effectuated as a sale by the Requesting Party and not effectuated as an exchange. The Requesting Party hereby agrees to indemnify, defend (with counsel reasonably satisfactory to the Non-Requesting Party) and hold harmless the Non-Requesting Party from and against any and all claims, loss, cost, damage, or expense (including, without limitation, reasonable attorneys' fees) incurred by the Non-Requesting Party and arising out of or relating to the Non-Requesting Party's participation in the Exchange.

[Remainder of Page Intentionally Left Blank]

Section 7.16 Entire Agreement. This Agreement and the attached exhibits, which are by this reference incorporated herein, and all documents in the nature of such exhibits, when executed, contain the entire understanding of the parties and supersede any and all other written or oral understanding.

IN WITNESS WHEREOF, Seller and Buyer have executed this Agreement as of the day and year first written above.

SELLER: **ISIS PHARMACEUTICALS, INC.**

By: /s/ B. Lynne Parshall
B. Lynne Parshall
Executive Vice President, CFO & Director

BUYER: **ELECTRO SURFACE TECHNOLOGY, INC.**

By: /s/ Hiroo Kirpalani
Name: Hiroo Kirpalani
Title: President

EXHIBIT A

DISCLOSURE STATEMENT

None

EXHIBIT B

PROPERTY DESCRIPTION

EXHIBIT D

LIST OF SERVICE AND EQUIPMENT CONTRACTS

[To be provided by Isis prior to execution of Agreement]

EXHIBIT E

DEED

Assessor’s Parcel No.

RECORDING REQUESTED BY
AND WHEN RECORDED RETURN TO:

MAIL TAX STATEMENTS TO:

The undersigned grantor declares:

Documentary transfer tax is:

o computed on full value of property conveyed, or
o computed on full value less value of liens and encumbrances.

GRANT DEED

FOR VALUABLE CONSIDERATION, the receipt and sufficiency of which are hereby acknowledged, ISIS PHARMACEUTICALS, INC., a Delaware Corporation, HEREBY GRANTS to Electro Surface Technology, Inc., a California Corporation, all that real property in San Diego County, California, described as follows:

SEE APPENIX "A" ATTACHED HERETO AND BY THIS REFERENCE INCORPORATED HEREIN.

This conveyance is made subject to all liens and encumbrances of record.

GRANTOR:

ISIS PHARMACEUTICALS, INC.

By: _____
B. Lynne Parshall
Executive Vice President, CFO & Director

Date: September , 2005

MAIL TAX STATEMENTS AS DIRECTED ABOVE

STATE OF CALIFORNIA)
) ss.
COUNTY OF)

CAPACITY CLAIMED BY SIGNER
Though statute does not require the Notary to fill in the data below, doing so may prove invaluable to persons relying on the document.

On , before me, ,
Personally appeared *(name of witness)*,

o personally known to me
-or-
o proved to me on the basis of satisfactory evidence to be the person whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity, and that by his/her/their signature(s) on the instrument the person(s) or the entity upon behalf of which the person(s) acted, executed the instrument.

o Individual
o Corporate Officer(s)
o Partner(s) o Limited o General
o Attorney-in-Fact
o Trustee(s)
o Guardian/Conservator
o Other:

Witness my hand and official seal.

_____
Signature of the Notary

SIGNER IS REPRESENTING:
Name of person(s) or entity(ies)

_____

This certificate must be attached to the document described at right:

Title or Type of Document: _____
Number of Pages: _____ Date of Document: _____
Signer other than named above: _____

EXHIBIT F

BILL OF SALE

FOR VALUABLE CONSIDERATION, the receipt and sufficiency of which are hereby expressly acknowledged, ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Seller"), hereby assigns, transfers and conveys to Electro Surface Technology, Inc. ("Buyer"), **WITHOUT WARRANTY, EXPRESS OR IMPLIED**, all of Seller's right, title and interest in and to that certain personal property described in the attached **Schedule 1** (the "Personal Property"). The foregoing conveyance is made pursuant to, and is subject to the terms and conditions of, that certain Agreement for Purchase and Sale of 2280 Faraday Avenue, San Diego, CA dated as of June 28, 2005, by and between Seller and Buyer.

IN WITNESS WHEREOF, Seller has executed this Bill of Sale as of , 20 .

SELLER:

ISIS PHARMACEUTICALS, INC.

By: _____
B. Lynne Parshall
Executive Vice President, CFO & Director

SCHEDULE 1

(Attach list of personal property)

APPENDIX A

[Attach legal description of real property]

EXHIBIT G

ASSIGNMENT OF INTANGIBLE PROPERTY

FOR VALUABLE CONSIDERATION, the receipt and sufficiency of which are hereby expressly acknowledged, ISIS PHARMACEUTICALS, INC.**,** a Delaware corporation ("Assignor"), hereby assigns, transfers and conveys to Electro Surface Technology, Inc., a California corporation ("Assignee"), all of Assignor's right, title and interest in and to the Intangible Property, as those terms are defined in that certain Agreement for Purchase and Sale of 2280 Faraday Avenue, Carlsbad, CA dated June28, 2005 (the "Agreement"), entered into by and between Assignor, as "Seller," and Assignee, as "Buyer."

In accordance with the Agreement, Assignee hereby assumes all obligations of owner of the Intangible Property arising on or after the date of this Assignment (collectively, the "Assigned Obligations").

IN WITNESS WHEREOF, Assignor and Assignee have executed this Assignment of Intangible Property as of September , 2005

ASSIGNOR:

ISIS PHARMACEUTICALS, INC.

By: _____
B. Lynne Parshall
Executive Vice President, CFO & Director

ASSIGNEES:

_____

By: _____
Its:

SCHEDULE 2.3(A)

ANALYTICAL METHODS FOR CORE TEST

EPA 8015M for Non-Halogenated Organics
EPA 8260B for Volatile Organic Compounds (VOC's)
EPA 8270C for Semi-Volatile Organic Compounds

SCHEDULE 4.2(C)

PARKING SPACES SUBJECT TO EASEMENT

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

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) 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

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2005

/s/ Stanley T. Crooke

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

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

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) 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

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2005

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

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, 2005, to which this Certification is attached as Exhibit 32.1 (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 9, 2005

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	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.